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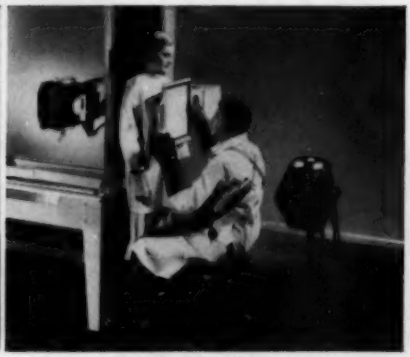

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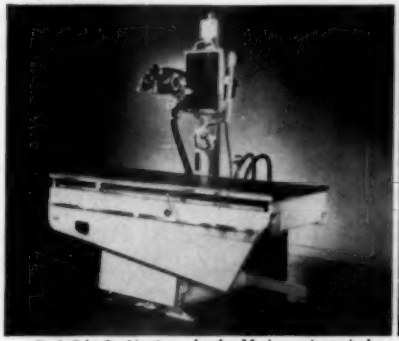

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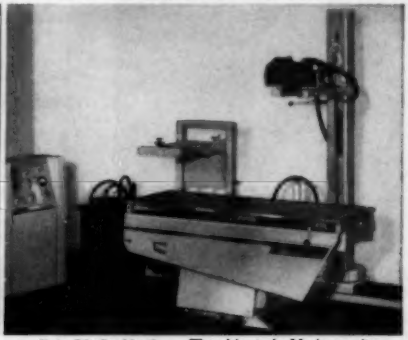

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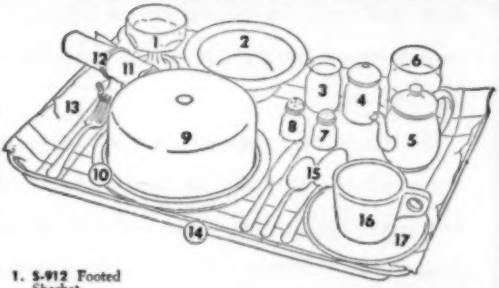

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ARTIFICIAL PNEUMOTHORAX: A STATISTICAL ANALYSIS OF 557 CASES INITIATED IN 1930–1939 AND FOLLOWED IN 1949[1, 2]

I. The Influence of Clinical Findings Before Induction on Early and Late Results

ROGER S. MITCHELL

(Received for publication March 30, 1951)

INTRODCUTION

Much experience with the artificial pneumothorax treatment of pulmonary tuberculosis has accumulated in the past fifty years (1–5). There is still, however, considerable disagreement about the indications for, and management of, this procedure.

Numerous observers have recorded that approximately 65 to 90 per cent of patients remain well for periods ranging from one to fifteen years after the abandonment of a previously "effective" pneumothorax (6–13). Emphasis has thus been placed upon the desirability of obtaining "effective" pneumothorax. Most reports, however, either fail to define adequately the term "effective" or define it simply as a collapse which produces cavity closure and sputum "conversion." In particular, the presence, extent, and location of pleural adhesions frequently are not mentioned (3, 5, 6, 14–21). Only a limited number of reports have emphasized the importance of the relationship between anatomic freedom of the lung from the adjoining structures and a satisfactory clinical response to pneumothorax (9, 10, 22–27).

Very few studies (16, 19, 28) have covered the entire clinical course of pneumothorax therapy, including early and late results and complications in a large group of patients in whom pneumothorax had been successfully induced. Comparisons of results observed in patients who received pneumothorax with results in those in whom no space could be found have yielded data of questionable value. This was true because the groups compared varied widely in background factors; were followed varying lengths of time or not long enough; or, in retrospect, frequently were poor candidates for pneumothorax therapy (2, 22, 29–31).

Coincident with the recent trend toward the use of thoracoplasty, pulmonary resection, and pneumoperitoneum as primary procedures, there has been a de-

[1] From Trudeau Sanatorium, Trudeau, New York.

[2] Presented, in part, before the Medical Session, as part of the *Clinical Session* at the 47th annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, on May 16, 1951.

crease in the number of patients subjected to artificial pneumothorax therapy (32). After a careful review of the literature, Rafferty has recently focused attention on the need for a reconsideration of the indications, contraindications, and management of pneumothorax (4).

The objective of the present study is not to evaluate pneumothorax, since there is no satisfactory control, but rather to measure the effect of various factors on the outcome of pulmonary tuberculosis treated with pneumothorax.

In retrospect, the indications for, and management of, pneumothorax induced ten to twenty years ago at Trudeau Sanatorium were frequently not in accord with current opinion. The difficult and treacherous problem of trying to demonstrate that results in this series were better or worse than those obtained elsewhere has therefore been avoided. An attempt to compare pneumothorax with other forms of treatment for pulmonary tuberculosis has been omitted for similar

TABLE 1

Source of Cases for Study

All pneumothorax attempts at Trudeau Sanatorium for 10 years: January 1, 1930 to December 31, 1939		589
No space found	116	
Abandoned in less than six months because of poor collapse; no early or late serious complications of pneumothorax	21	
Total unsuccessful	137	
Number of cases successfully induced at the Sanatorium		452
Number of cases successfully induced elsewhere within the three months prior to admission and in this same ten-year period		153
Total pneumothorax "cases" in the ten-year period		605
Excluded from analysis for reasons outlined below	48	
Cases studied statistically		557

reasons. The wide variety in indications and management, on the other hand, made it profitable to study the effect, if any, of these variables upon results.

The present report outlines the source material, general methods of study, and over-all results; it includes a discussion of case selection, about which there is still considerable disagreement (32). Four subsequent reports based on the same series of patients will include discussion of the question of management and the problems relating to the contralateral lung, empyema, and the unexpandable lung. The interrelation and practical application of these findings will be the subject of the sixth and final report.

MATERIAL AND METHODS

The study is based upon all Trudeau Sanatorium patients in whom pneumothorax was attempted during the ten-year period between January 1, 1930 and December 31, 1939. In order to avoid any bias, simultaneous bilateral pneumothorax was included and counted as two "cases"; 14 patients in this series were

so treated; another 11 of the cases studied received contralateral pneumothorax after abandonment of the first side.

Pneumothorax was attempted in 589 "cases" at Trudeau Sanatorium during this ten-year period (table 1). In 137 (23 per cent) of these, either the attempts were unsuccessful or pneumothorax was abandoned as unsatisfactory but *without complications* within the ensuing six months. A collapse not maintained for six months or more was excluded as representing an inadequate trial of pneumothorax.

The remaining 452 "cases" (589 minus 137) plus 153 initiated before admission and during the ten-year period (605 in all) make up the basic material for the study. The 153 cases induced before admission were included in order to study: (a) an unselected consecutive series of cases and (b) the effect of widely varying indications upon the outcome of pneumothorax treatment.

After due consideration, 48 of the 605 cases were excluded from the analysis for the reasons specified below:

Supplementary phrenic nerve interruption early in the course of pneumothorax	36
Pneumonolysis, producing clinically effective collapse, delayed for more than one year after pneumothorax induction	8
Insufficient data from which to determine initial therapeutic results	4
	48

This left 557 "cases" (or 532 patients, including the 25 bilateral cases) upon which the statistical analyses were based.

The clinical records and all available chest roentgenograms taken before, during, and after treatment at Trudeau Sanatorium were reviewed in each of these 605 cases. Details of the clinical course in the years following discharge were obtained from records of readmission to Trudeau Sanatorium; from routine yearly follow-up questionnaires to ex-patients; from reports and films obtained from physicians, various institutions, and health departments; and finally from replies to special questionnaires sent by the writer to all living ex-patients in the study. When roentgenograms were insufficient in number, technically inadequate, or unavailable, the interpretations of the radiologist contained in the clinical records were utilized in so far as possible.

Time of evaluation: Each case was evaluated at three points in the clinical course: (a) *one year after induction,* (b) *at abandonment, and* (c) *three years after abandonment.*

Criteria for classification of results:

The criteria of a *"good" result at one year after induction* were the attainment of all of the following:

a. Disappearance of all homolateral cavities, if present, as interpreted from serial single and stereoscopic chest roentgenograms.
b. Clearing and/or contraction of infiltration.
c. No empyema.
d. No significant spread or increase of disease in the contralateral lung (See Discussion).

e. Conversion of positive sputum to negative on two or more consecutive fifty-hour concentrated sputum smears.

A *"poor" result at one year* after induction was defined as failure to meet all the criteria of a "good" result at one year.

Empyema was defined as a cloudy or grossly purulent pleural fluid, positive for acid-fast organisms in concentrated specimen, or *M. tuberculosis* on culture.

A *"good" result at abandonment* was a "good" result at one year, which had not developed homolateral empyema or "significant" reactivation of disease in either lung during the period of continuation of pneumothorax and until approximately three months after the last refill.

A *"significant" reactivation* was defined as an increase of disease which eventuated in some form of active treatment in a sanatorium or at home.

TABLE 2

Yearly and Cumulative Rates of Reactivation After Abandonment of Pneumothorax in 249 Patients Whose Response to Pneumothorax Had Been Entirely Satisfactory Through the Period of Collapse and Abandonment

(By the Life-Table Method)

YEAR AFTER ABANDONMENT	PRESENT AT BEGINNING OF YEAR	REACTIVATION DURING YEAR	WITHDRAWN DURING YEAR	AVERAGE NUMBER AT RISK DURING YEAR	PERCENTAGE OF REACTIVATIONS DURING YEAR	PERCENTAGE WITHOUT REACTIVATION DURING YEAR	CUMULATIVE PERCENTAGES OF REACTIVATIONS AT EACH YEAR
1	249	9	7	245.5	3.7	96.3	3.7
2	233	15	10	228	6.6	93.4	10.1
3	208	8	7	204.5	3.9	96.2	13.6
4	193	3	3	191.5	1.6	98.4	15.0
5	187	2	10	182	1.1	98.9	16.0
6	175	1	13	168.5	0.6	99.4	16.5
7	161	0	21	150.5	0	100	16.5
8	140	0	13	133.5	0	100	16.5
9	127	0	18	118	0	100	16.5
10	109	0	22	98	0	100	16.5
11	87	1	15	79.5	1.3	98.7	17.6
12	71	0	17	62.5	0	100	17.6
13	54	0	14	47	0	100	17.6
14	40	0	15	32.5	0	100	17.6
15	25	1	10	20	5	95	21.7
16	14	0	10	9	0	100	21.7
17	4	0	3	2.5	0	100	21.7
18	1	0	1	0.5	0	100	21.7

A *"poor" result at abandonment* was defined as failure to meet the criteria of a "good" result at abandonment.

A *"good" result at three years after abandonment* was a "good" result at *both* one year after induction *and* at abandonment, following which the patient did not develop empyema or did not show a "significant" (defined above) reactivation of disease in either lung during the first three years after abandonment. The reason for using a three-year follow-up period is shown in table 2.

Table 2 is based upon the yearly and cumulative post-abandonment reactivation rates in the 249 patients whose response to pneumothorax had been entirely satisfactory through the period of collapse and immediately after abandonment.

The cumulative rate of reactivation, projected by the life-table method through eighteen years after abandonment, was 21.7 per cent; it was 13.6 per cent after three years, the point at which the curve begins to flatten. The mean duration of follow-up after abandonment in these 249 cases was 9.4 years. Figures obtained by the life-table method did not agree with the gross figures (40 of 249, or 16 per cent) but are considered much more reliable (33).

A *"poor" result at three years after abandonment* was defined as failure to meet the criteria of a "good" result at three years after abandonment.

In other words, a case was classified as a "poor" result because of failure to control the homolateral disease either during the first year after induction or at the time of initial reactivation of disease, whichever occurred first. The use of the term "poor" pneumothorax result may be confusing; it is recognized that some patients whose initial response to pneumothorax was poor occasionally derived benefit from the continued collapse even though all the criteria of a "good" result were not met.

The background features of the patient population merit a brief description. Most of the patients were young adults, although the age distribution was from 16 to 61 with a mean of 29 years. There were a few more males (53 per cent) than females. All except 2 of the patients were white with a preponderance of Northern European ancestry. The most notable feature was a socio-economic background considerably higher than is found in municipal sanatoriums. Infrequency of complications also made this a rather select group: 9 per cent had intestinal (all patients had routine barium motor-meal examinations), 6 per cent laryngeal, and 4 per cent other extrapulmonary tuberculosis exclusive of disease of the bronchi and pleura. Nontuberculous complications were also rare: 5 patients had diabetes; 4, peptic ulcer; 2, pregnancy; 2, cardiac disease; 1, asthma; 1, hypertension; 1, silicosis; and 1, pituitary dysfunction.

In the course of making this analysis, the data were studied by the so-called master-table technique. The master table is a series of ultimate subdivisions of each factor; e.g., young females with disease of moderately advanced extent and no cavity in whom a satisfactory collapse was achieved, and so forth. The incidence of "good" results in each final subdivision was then studied for hidden facts and correlations. Many of the final subdivisions contained no or only a very few cases. After making the initial observation on the smallest subdivision, the data were recombined in various ways in accord with the findings and clinical judgment.

The statistical analyses were carried out by means of mechanical sorting and tabulation of business machine punch cards, each having eighty columns of ten variables each. The differences between these percentages were then tested for statistical significance. When two percentages were compared, the standard error of the difference between the two percentages was computed with standard formulas (34). When the ratio $\frac{\text{observed difference}}{\text{standard error of difference}}$ was 3.0 or more, the difference was considered *significant*; when this ratio fell between 2.5 and 3.0, the difference was considered *probably significant*. When this ratio was below 2.5, the difference was considered *not significant*.

When three or more percentages were compared, the chi-square method was used. When "P" (probability) was 0.0026 or less, the differences were considered *significant*; when

"P" was 0.0027 to 0.012, the differences were considered *probably significant*; when "P" was 0.013 or higher, the differences were considered *not significant*. These probabilities by the chi-square method correspond to those used with the standard error method.

Both the standard error and chi-square criteria for *significant* mean that there is less than one chance in 370 of the difference occurring by chance. When these values were classified as *probably significant*, there is less than one chance in 80 of the difference occurring by chance. When these values were classified as *not significant*, there is *more* than one chance in 80 of the difference occurring by chance.

When a carefully planned study yields a good trend which is found, however, to be non-significant, it is considered good statistical practice to de-emphasize the mathematical tests.

OVER-ALL RESULTS

The total incidence of "poor" results with pneumothorax, as defined, was 340 of 557, or 61 per cent. The incidence of "poor" results at various stages of treatment was as follows: *during the first year after induction*, 241 (43.3 per cent) of the entire 557 cases; *during the rest of the period of collapse*, 42 (13.3 per cent)

TABLE 3

The Location of the Initial Failure or Reactivation of Disease from the Time of Induction to Three Years After Abandonment of Pneumothorax

THE LUNG RESPONSIBLE FOR "POOR" RESULT	STAGE OF THERAPY					
	First 12 months after induction		From first 12 months to abandonment		First 3 years after abandonment	
	Number	Per cent	Number	Per cent	Number	Per cent
Homolateral	127	53	18	46	25	54
Contralateral	29	12	22	52	11	23
Bilateral	83	35	1	2	11	23
Undetermined	2	—	1	—	2	—
Total	241	100	42	100	49	100

of the 316 still classified as "good" after the first year; *co-incident with abandonment*, 17 (6 per cent) of the 262 which were still "good" just before abandonment; in 12 cases still classified as "good" the patients were still receiving pneumothorax refills within three years of the end of the study. The post-abandonment rate of reactivation is shown in table 2.

The lung in which initial failure (homolateral) or reactivation of disease occurred is shown in table 3. The contralateral lung alone was apparently involved in 60 of the "poor" results and was part of a bilateral reactivation in 90 additional cases. The incidence of homolateral only versus contralateral and bilateral reactivation showed little fluctuation at the three stages of therapy.

In table 4 may be seen a record of all known surgical and other collapse therapy used in addition to pneumothorax in treating the "poor" results during the ensuing ten to twenty years.

Outlined in table 5 are the reasons given for abandonment of pneumothorax in the *508* cases in which refills are *known* to have been terminated. Attention

is called to the fact that "successful completion of therapy" was the reason given for abandonment in 38 cases classified as "poor" results at the end of the first year. Of these, 25 patients remained well after abandonment and 13 had relapses.

The status of the 532 patients (557 "cases") in 1949 may be seen in table 6. Sixty-one per cent were living and well; 5 per cent were able to do some work;

TABLE 4

Surgical and Other Collapse Therapy Known to Have Been Used in the Ensuing Ten to Twenty Years in 557 Cases Previously Treated with Pneumothorax

	HOMOLATERAL LUNG	CONTRALATERAL LUNG
Oleothorax	24	2
Phrenic nerve interruption	17	5
Pneumothorax	9*	8†
Thoracoplasty	54	9
Resection	5	2
Other surgical procedures	6	1

* Pneumothorax re-established.
† Induced after December 31, 1939.

TABLE 5

Reasons Given for Abandonment of Pneumothorax

	NUMBER	PER CENT
"Successful completion of therapy"	258	51
At patient's insistence	21	4
Technically poor collapse	16	3
Poor result: homolateral	32	6
Spread of disease: contralateral	43	9
Empyema	68	13
Persistent pleural effusion	40	8
Obliterative pleuritis	12	2
Reason not known	18	4
Total pneumothorax "cases" abandoned	508	100

7 per cent were chronically ill with tuberculosis; 26 per cent were dead; contact had been lost in 1 per cent.

The Relationship of Pre-Induction Clinical Findings to Results

In tables 7 through 17, which cover the relationship of pre-induction clinical findings to results, various cases are necessarily excluded because of the lack of pertinent data.

Chronology: The ten-year study period was divided into five two-year periods. Early and late results and the number of new cases per two-year period did not vary greatly during the first four two-year periods. In the period 1938–1939,

however, the number of new cases fell to about one-half the mean figure for the four previous two-year periods, although the total admissions remained about the same. In this proportionately smaller number of admissions treated with pneumothorax, late results were significantly better than in the 1930–1937 cases.

TABLE 6

1949 Status of the 532 Patients in Whom Pneumothorax Was Induced in 1930–1939

	NUMBER	PER CENT
Working and Well		
Pneumothorax abandoned for 3 years or more	307	57
Pneumothorax abandoned in 1946–1949	11	2
Pneumothorax still continued in 1949	8	2
Working part time, tuberculosis presumably healed, but patient partly disabled	24	5
Chronically ill with tuberculosis	36	7
Dead: tuberculosis	119	22
Dead: nontuberculous causes	21	4
Contact lost	6	1
Total patients	532	100

TABLE 7

Relationship of Age of the Patient to Late Results

AGE	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
16–25	219	99	45.2
26–33	220	80	36.4
34+	93	25	26.9
Total	532	204	

Probably significant.

Place of induction: There was no essential difference in results between cases with pneumothorax induced before admission to Trudeau Sanatorium and those induced after admission.

Sex: There were 294 male and 263 female "cases" in the series. Results were not found to vary particularly with the sex of the patient.

Age: Age appeared (table 7) to have some relationship to late results; the poorest results occurred in persons 34 years of age or older. This experience is contrary to the generally acknowledged instability and uncertain course of tuberculosis in young adults. Peters and associates, on the other hand, have reported that the patient's age had no bearing on results with pneumothorax (20).

Side of pneumothorax: Results were approximately the same with right and left pneumothorax.

Race: No analysis of the effect of racial differences was made because the patients were predominantly of the Caucasian race, with no Negroes and only 2 Orientals in the group.

Age of disease: An estimate of the age of the disease under treatment was based upon the duration and nature of symptoms and the character of the roentgenographic shadows in serial films, including those taken months or years before admission. In deciding that a lesion was "old," attention was paid in particular to evidence of pulmonary contraction, stringlike and calcific densities, and patches of emphysema. A lesion was classified as of "medium" duration when the various considerations placed it somewhere between "recent" and "old." In very few cases of this series were the lesions dated by a previous negative film so that the "age of disease" was at best a rough estimate.

TABLE 8

Relationship of Estimated Age of Disease to Late Results

ESTIMATED AGE OF DISEASE	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
"Recent"	309	126	} *40.5*
"Medium"	160	64	
"Old"	26	5	*19.2*
Total	495		

Probably significant.

Late results in "old" disease were less favorable than in disease of "recent" or "medium" duration (table 8). Similar findings with regard to age of disease have been made previously (35, 36, 37).

Dynamic status: By dynamic status is meant the clinical and roentgenographic trend of the pulmonary disease during the one to twelve months before induction. Data were not available in 147 cases, principally because pneumothorax was induced very soon after diagnosis. In table 9 it is shown that this factor had no particular relationship to late results.

Nonbronchoscopic indications of endobronchial disease: The continued presence of tubercle bacilli in the sputum in the absence of manifest cavity was considered suggestive of active endobronchial tuberculosis. In any event, late results in noncavitary cases were considerably less favorable than in cavitary disease (table 10). The differences were not statistically significant, however, until the period three years after abandonment. Results with pneumothorax in noncavitary disease have previously been reported as relatively unfavorable (3); the reverse has also been reported (8).

Certain other roentgenographic findings may be considered suggestive of major

endobronchial disease (4): (*1*) lobar distribution of disease; (*2*) contracted lobe or lung; (*3*) bronchiectasis as demonstrated by bronchogram; and (*4*) negative or almost negative chest roentgenograms in the presence of sputum persistently positive for tubercle bacilli.

Results in cases coming under these categories were less favorable than in those cases not exhibiting these findings (table 11). This difference, while not statistically significant three years after abandonment, is not in conflict with public opinion.

TABLE 9

Relationship of Dynamic Status of Disease to Late Results

DYNAMIC STATUS	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Improving	70	23	*32.9*
Same	77	33	*42.9*
Worse	248	91	*36.7*
Total	395		

Not significant.

TABLE 10

Relationship of Presence or Absence of Cavity to Early and Late Results

CAVITY ON STEREOSCOPIC FILMS	CUMULATIVE "GOOD" RESULTS								
	At the end of the first year			At abandonment			At three years after abandonment		
	Evaluable cases	"Good"		Evaluable cases	"Good"		Evaluable cases	"Good"	
		Number	Per cent		Number	Per cent		Number	Per cent
Present	481	278	*57.8*	470	218	*46.4*	462	189	*40.9*
Absent	76	38	*50.0*	75	27	*36.0*	70	15	*21.4*
Total	557			545			532		
	Not significant.			Not significant.			Significant.		

Clinical indications of endobronchial disease, such as wheeze and severe nonproductive cough, could not be considered in this report because little attention was being given in the clinical records to the possibility of this complication until the late nineteen thirties.

It was not feasible to compare the effect of positive and negative bronchoscopic findings on results with pneumothorax because only *17* of the 557 cases were bronchoscoped prior to the induction of pneumothorax.

There was no important relationship between the presence of a *fluid level* within a cavity and results.

Location of disease: The results of pneumothorax treatment for cavity in various locations in the lung are compared in table 12; cases having no cavity, or having cavities in multiple locations, were excluded. The four locations were chosen roughly, and localization was determined without the aid of lateral films or planigrams.

The differences in results favored lesions in the lower lung fields. As will be reported later (38), however, it should be stressed that there was a much greater chance of a satisfactory anatomic collapse in this series of cases when the

TABLE 11

Relationship of Roentgenographic Evidence of Major Bronchial Disease to Late Results

ROENTGENOGRAPHIC EVIDENCE OF MAJOR BRONCHIAL DISEASE	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Present	35	8	*22.9*
Absent	375	150	*40.0*
Total	410		

Not significant.

TABLE 12

Relationship of Location of Cavity to Late Results

LOCATION OF CAVITY	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Apex	118	42	*35.6*
Infraclavicular	220	89	*40.5*
Mid-lung	90	42	*46.7*
Base	20	10	*50.0*
Total	448		

Not significant.

disease was located predominantly in the mid and lower lung rather than concentrated in the apex and infraclavicular area.

Cavity size: While table 13 shows an apparent strong relationship between cavity size and results, study of this factor by means of a master table negated this observation as follows. When cases of comparable degree of roentgenographic density and type of collapse (38) were studied individually, cavity size had no relationship to results. This has been the experience of others (3, 22).

Single versus multiple cavitation: The results with cavities which were multilocular and/or multiple were slightly less favorable than with those which were single.

Cavity wall: There was no relationship between the thickness of the cavity "wall" by roentgenogram and the result obtained (table 14). Examples of these three types of cavity "wall" are shown in figure 1. The classification was made roughly; when the "wall" was obscured by dense surrounding disease, the case was excluded from the study.

Extent of disease: There was an important difference between results in far advanced and in moderately advanced disease (table 15). Pneumothorax was

TABLE 13

Relationship of Cavity Size to Late Results

CAVITY SIZE (CM.)	CUMULATIVE "GOOD" RESULTS								
	At the end of the first year			At abandonment			At three years after abandonment		
	Evaluable cases	"Good"		Evaluable cases	"Good"		Evaluable cases	"Good"	
		Number	Per cent		Number	Per cent		Number	Per cent
0.5–3.0	357	223	*62.5*	354	178	*50.3*	347	157	*45.2*
3.5–6.0	87	44	*50.6*	82	30	*36.6*	76	23	*30.3*
6.5+	16	2	*12.5*	16	2	*12.5*	16	2	*12.5*
Total...	460			452			439		
		Significant.			Significant.		Probably significant.		

TABLE 14

Relationship of Thickness of Cavity "Wall" by Roentgenogram to Late Results

CAVITY "WALL" ESTIMATION FROM ROENTGENOGRAM	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
"Thin".....	108	42	*38.9*
"Medium".....	95	50	*52.6*
"Thick".....	103	40	*38.8*
Total.....	306		
		Not significant.	

used to treat only 2 cases of minimal disease in the ten-year period forming the basis of the study.

Density of roentgenographic shadows: A very strong relationship was found between results and the character of the disease as reflected by the density of the roentgenographic shadows (table 16). In simple terms, when the roentgenograms were technically comparable, the lighter the shadows, the more likely a good result. This observation has presumably been repeatedly made but, in most reports, the distinction is made between "exudative" and "productive" disease. Scattered or isolated nodular or linear shadows from 1 to 5 mm. in diameter were classified as "light." Multiple, confluent dense shadows of approximately

2 cm. or more in diameter were classified as "heavy." Shadows falling between these extremes were classified as "medium." Examples of the three degrees of roentgenographic density used here are given in figure 2.

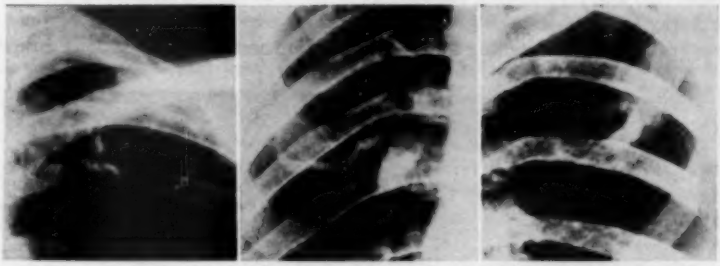

FIG. 1. Examples of (A) "thin," (B) "medium," and (C) "thick" cavity "wall"

TABLE 15

Relationship of Extent of Disease to Late Results

NATIONAL TUBERCULOSIS ASSOCIATION CLASSIFICATION	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Moderately advanced	370	158	*42.7*
Far advanced	160	45	*28.1*
Total	530		

Significant.

TABLE 16

Relationship of the Density of the Roentgenographic Shadows to Late Results

DENSITY OF ROENTGENOGRAPHIC SHADOWS	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
"Light"	58	38	*65.5*
"Medium"	157	70	*44.6*
"Heavy"	171	46	*26.9*
Total	386		

Significant.

Contralateral lung: The extent and activity of the disease in the contralateral lung (table 17) were found to be closely related to results and quite in accord with the experience of others (3, 20, 39).

Prior bed rest: The effect of the duration of bed rest prior to induction of

pneumothorax was studied in various ways. Studied alone, without consideration of factors predetermining the duration of prior bed rest, there was no apparent relationship to either early or late results. This was the experience of Myers (40) and presumably the opinion of other advocates of ambulatory pneumothorax (41–44). In addition, when the cases were subdivided into groups of comparable extent according to the National Tuberculosis Association classifica-

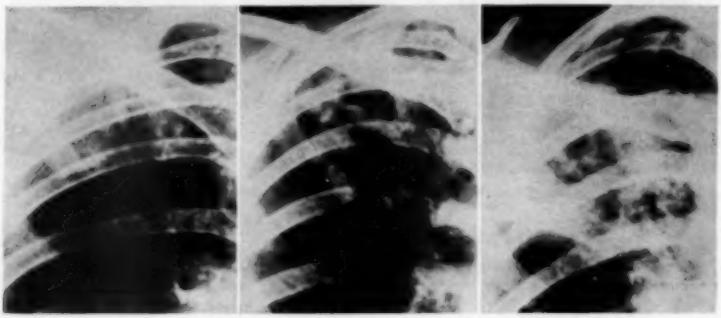

FIG. 2. Examples of (A) "light," (B) "medium," and (C) "heavy" roentgenographic shadows.

TABLE 17

Relationship of Condition of Contralateral Lung to Late Results

CONTRALATERAL LUNG	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Negative	156	77	*44.8*
Minimal	174	71	*40.8*
Advanced inactive	37	13	*35.1*
Advanced, active	165	43	*26.0*
Total	532		

Significant.

tion or by cavity size, a correlation between the duration of prior bed rest and results could still not be demonstrated.

Interrelation of factors: The possibility of a relationship between any two of the various factors studied herein was closely studied by means of a master table. The disease in the contralateral lung was found to be more extensive, the older the estimated age of the disease in the homolateral lung. No other important relationship could be demonstrated between any of the various factors. Furthermore, many other studies, such as results according to sex after elimina-

tion of the factor of age and results according to duration of prior bed rest and thickness of cavity wall after elimination of the factors of extent of disease and density of the roentgenographic shadows, failed to yield additional useful information.

DISCUSSION

It must be emphasized that the actual percentages of "good" results are not important; attention is directed instead to the *differences* between the percentages in each table for the reasons outlined in the Introduction.

There will doubtless be disagreement with the inclusion of activation of disease *apparently confined* to the contralateral lung as failure of unilateral pneumothorax. Is it not logical to conclude, however, that satisfactory collapse in the correct pulmonary planes will speed the healing process and so reduce materially the chances of the dissemination of the disease to the contralateral lung? On the other hand, an unsatisfactory collapse may not produce adequate relaxation of the diseased area, but may principally compress healthy lung tissue; under such circumstances, the chances of extension of the disease to the contralateral lung may be materially greater. In this connection, evidence will be presented in a subsequent report (tables 5, 6, 7 (45)) to show that there is a significant relationship between the incidence of contralateral reactivation and the degree of freedom from adhesions of the collapsed lung.

The additional information now provided by planigraphy indicates that the disappearance of cavity on the single or stereoscopic film is not always a reliable criterion of actual cavity closure. Unsuspected persistence of cavity may account for many otherwise unexplained bronchogenic disseminations of disease in either lung.

Finally, a study of the patient as a whole rather than of a single lung appears to be the most practical method of comparing the effectiveness of any two forms of treatment for pulmonary tuberculosis. Certainly, as far as the patient is concerned, a purely contralateral reactivation is as much a failure of pneumothorax as is a homolateral or bilateral reactivation. For these reasons, contralateral activation (see table 3) is included as evidence of a failure of unilateral pneumothorax.

Attention is directed to the low incidence (6 per cent) of reactivation of disease coincident with the abandonment of pneumothorax. This figure includes only reactivations occurring in those cases which had shown a good clinical response to pneumothorax up to that time. It is possible that some reactivations, coincident with a *trial* of abandonment and then controlled by immediate reestablishment of pneumothorax, were not reported. If this was known to have taken place, however, it was classified as a relapse at abandonment in this study. An incidence of 8 per cent reactivations at abandonment has previously been reported (13).

While there was no demonstrable relationship between results and the duration of prior bed rest, the incidence of empyema was found to be significantly

higher with little or no prior bed rest, as will be reported later (46). Furthermore, an unduly large proportion of the patients were given pneumothorax within one to four weeks after diagnosis. This group contained not only those who would have done well without pneumothorax, but also those with disease considered in those days too acute or extensive to justify undue delay. In addition, many of those who received prolonged bed rest before induction may have had a poorer than average prognosis because a progression of disease had often occurred *during* bed-rest treatment. The findings with regard to prior bed rest are therefore considered inconclusive.

Attention is drawn to the most important factor in the selection of cases for pneumothorax in this series, namely, the relative density of the roentgenographic shadows (table 16). This factor is interpreted as a fairly reliable measure of the severity of the inflammatory component of the tuberculous process. In the light of the findings, it may well be demonstrated that the effectiveness and safety of pneumothorax will be increased by the use of chemotherapy for a period prior to induction of pneumothorax in those cases with the dense shadows of acute pneumonic disease.

As was found in studying late results after phrenic nerve interruption (47), the location of cavity did not bear a close relationship to results (table 12). The location of cavities within lobes or the proximity of cavities to the periphery of the lung, however, were not established in this study because of the lack of lateral films and of planigrams.

SUMMARY

Five hundred and fifty-seven consecutive cases of pulmonary tuberculosis treated with pneumothorax, induced over a ten-year period from 1930 through 1939, were studied from the time of diagnosis until 1949 or death and then subjected to a statistical analysis. Contact was lost in only 1 per cent of the series.

According to the criteria used in this study, 43 per cent of cases failed to respond satisfactorily to pneumothorax during the first year after induction; 17 per cent of those still satisfactory after one year had initial reactivation of disease between this time and soon after abandonment of pneumothorax (only 6 per cent of those still satisfactory at abandonment had reactivation at that time); 22 per cent of those still satisfactory after abandonment had initial reactivation within the ensuing three to sixteen years.

An important relationship was found between late results with pneumothorax and the following factors: age of the patient; estimated age of disease; extent and density of pulmonary infiltration; roentgenographic evidence of endobronchial disease; presence of tubercle bacilli in the sputum in the absence of cavity; and the extent and activity of disease in the contralateral lung.

No significant relationship was found between late results with pneumothorax and the following factors: sex; side of pneumothorax; location of cavity; thickness of the cavity wall; and the presence of a fluid level within a cavity.

The reasons for inability to demonstrate a relationship between results and the duration of prior bed rest are discussed.

SUMARIO

Neumotórax Terapéutico: Análisis Estadístico de 557 Casos Iniciados en 1930–1939 y Reobservados en 1949. I. Influyo en los Resultados Tempranos y Tardíos de los Hallazgos Clínicos Anteriores a la Inducción

Quinientos cincuenta y siete casos consecutivos de tuberculosis pulmonar tratados con neumotórax inducido durante el decenio de 1930 a 1939 fueron estudiados desde la fecha del diagnóstico hasta 1949 o el fallecimiento, y sometidos luego a un análisis estadístico. Sólo se perdió de vista a 1 por ciento.

Conforme a las pautas utilizadas en este estudio, 43 por ciento de los casos no respondieron satisfactoriamente al neumotórax durante el primer año después de la inducción; 19 por ciento de los que eran todavía satisfactorios al cabo de un año tuvieron reactivación inicial de la enfermedad entre dicha fecha y poco después del abadono del neumotórax; y sólo 6 por ciento de los que eran todavía satisfactorios al abandonarse el neumotórax tuvieron reactivación inicial durante los tres a dieciséis años siguientes.

Descubrióse una importante relación entre los resultados tardíos del neumotórax y los siguientes factores: Edad del enfermo, edad calculada de la afección, extensión y espesor de la infiltración pulmonar, signos radiográficos de enfermedad endobronquial, positividad del esputo en ausencia de cavernas y extensión de la enfermedad en el pulmón contralateral.

No se observó mayor relación entre los resultados tardíos del neunotórax y los siguientes puntos: Sexo, lado, localización de la caverna, espesor de la pared de la caverna y presencia de un nivel de líquido dentro de una caverna.

Discútense las razones por las que no se pudo descubrir relación entre los resultados y la duración del previo reposo en cama.

RESUME

Pneumothorax artificiel: Analyse statistique de 557 cas instaurés en 1930–1939 et réexaminés en 1949. I. Influence des conditions cliniques existantes avant la création du pneumothorax sur les résultats immédiats ou éloignés

Une série consécutive de 557 cas de tuberculose pulmonaire traités par le pneumothorax pendant une période de plus de dix ans, de 1930 jusqu'à 1939 inclusivement, a été étudiée depuis le moment du diagnostic jusqu'à 1949 ou jusqu'au décès du patient; ces cas ont été ensuite soumis à l'analyse statistique. La proportion des malades qui n'a pu être suivie s'élève à 1%.

Selon les critères utilisés dans cette étude, 43% des cas n'ont pas réagi favorablement au pneumothorax pendant la première année qui a suivi son institution; un an après la création du pneumothorax, 19% des cas considérés comme satisfaisants ont présenté des signes de réactivation de la tuberculose entre ce moment et tôt après l'abandon du pneumothorax (parmi les cas encore satisfaisants après l'abandon du pneumothorax 6% seulement ont présenté des signes de réactivation au cours des trois à seize années suivantes).

Une corrélation marquée a été observée entre les résultats éloignés du pneumothorax et les conditions suivantes: âge du malade, nombre d'années écoulées

depuis le début de l'affection; étendue et densité de l'infiltration du poumon; signes radiologiques de lésions endobronchiques; présence de bacilles dans les crachats, en l'absence de cavernes visibles; étendue des lésions dans le poumon opposé.

Aucune corrélation n'a été observée entre les résultats tardifs du pneumothorax et les conditions suivantes: Sexe, côté pulmonaire affecté, siège de la caverne, épaisseur de la paroi de la caverne, présence d'un épanchement intracavitaire.

Les raisons qui expliquent l'impossibilité de démontrer un rapport entre les résultats et la durée de la période de repos au lit précédant l'institution du pneumothorax sont étudiées.

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ARTIFICIAL PNEUMOTHORAX: A STATISTICAL ANALYSIS OF 557 CASES INITIATED IN 1930–1939 AND FOLLOWED IN 1949[1, 2]

II. The Fate of the Contralateral Lung

ROGER S. MITCHELL

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INTRODUCTION

The fate of the contralateral lung during pneumothorax therapy apparently has been given only limited attention in the medical literature (1, 2, 3). By means of spirometric and bronchospirometric studies, Birath has shown that the contralateral lung may be appreciably collapsed by pneumothorax (4). Lucacer has even recommended contralateral pneumothorax when pleural symphysis prevents the use of pneumothorax on the side in need of collapse (5).

This report is a further study of 557 cases of pneumothorax initiated between 1930 and 1939 and followed to death or to 1949. These data, tables 5, 6, and 7 in particular, are presented in support of opinions expressed under "Discussion" in the first report of this series (6). Details on methods, definitions of terms, and criteria of statistical significance are also available in the first report.

In the 557 cases, 283 were found to have had "significant" reactivation[3] of pulmonary disease in one or both lungs or to have failed to improve on the pneumothorax side during the period between induction and abandonment. In these 283 cases, duration of pneumothorax ranged between six months and more than thirteen years; very few pneumothoraces were maintained for less than two years, and the average duration was approximately four years. An initial reactivation occurred *after* abandonment of pneumothorax in 40 cases; these may have been too remote and were excluded from consideration in the present report.

The 283 reactivations of disease were distributed as follows: 145 homolateral; 51 contralateral; 84 bilateral; and 3, insufficient details for classification. Bilateral reactivation is classified in this study as a form of contralateral reactivation. Therefore, the term "contralateral reactivation" hereafter includes both contralateral and bilateral reactivations of disease.

Various aspects of the disease in each lung were studied before induction of pneumothorax, as was their relationship to the incidence of contralateral reactivation during the period between induction and abandonment. Some cases were necessarily excluded from certain of the tables because pertinent data were lacking.

[1] From Trudeau Sanatorium, Trudeau, New York.

[2] Presented, in part, before the Medical Session, as part of the *Clinical Session* at the 47th annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1951.

[3] "Significant" reactivation of disease was defined as any increase of disease which eventuated in some form of active treatment in a sanatorium or at home. The term, reactivation, is used in relation to the disease as a whole and not necessarily to the contralateral lung.

RESULTS

Extent and activity of disease in the contralateral lung: Contralateral reactivation occurred much less frequently when that lung was roentgenographically normal before induction (table 1). In the presence of any visible infiltration, "active" disease was much more apt to exacerbate than "inactive" disease (table 2). Disease was classified as "active" in the presence of cavity or clear evidence of a changing lesion in serial films before induction. Findings of uniformly calcific or unchanging, circumscribed, nodular and string-like densities were considered evidence of an "inactive" lesion.

TABLE 1

Relationship of Extent of Disease in Contralateral Lung to Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained

CONTRALATERAL LUNG: EXTENT OF DISEASE	CASES		CONTRALATERAL REACTIVATION			
			Number		Per cent	
No disease seen	172		21		12.2	
Minimal	182	385	63	114	34.6	29.8
Advanced	203		51		25.1	
Total	557		135			

Significant.

TABLE 2

Relationship of Activity of Disease in Contralateral Lung to Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained

CONTRALATERAL LUNG: ACTIVITY OF DISEASE	CASES	CONTRALATERAL REACTIVATION	
		Number	Per cent
"Inactive"	93	6	6.4
"Active"	292	108	37.0
Total	385	114	

Significant.

The extent of the contralateral lesion, on the other hand, exhibited an unexpected relationship to the incidence of contralateral reactivation. Without consideration of the relative activity of the lesions, there was a slightly higher incidence of exacerbation of minimal than of advanced contralateral lesions (table 1). Jennings and Mattill have reported that there is a 6 per cent chance of contralateral spread if the contralateral lung is apparently free of disease at induction, a 21 per cent chance of its becoming worse if involved without cavity, and a 41 per cent chance of exacerbation if cavity is present (1).

Character of the disease in the homolateral lung: Paralleling the over-all results with pneumothorax (6), the density of the roentgenographic shadows in the

homolateral lung was found to have a very strong relationship to the incidence of contralateral reactivation (table 3). Examples of the three degrees of shadow density may be found in figure 2 of the first report of this series (6).

Location of the disease in the homolateral lung: In contrast to the findings of others (3), the predominant location of the disease in the collapsed lung was unrelated to the incidence of contralateral reactivation (table 4). In the table, "upper" is applied to the apex and infraclavicular regions; "lower" applies to the mid-lung and base.

TABLE 3

Relationship of Density of Roentgenographic Shadows in the Homolateral Lung to Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained

HOMOLATERAL LUNG: DENSITY OF ROENTGENOGRAPHIC SHADOWS	CASES	CONTRALATERAL REACTIVATION	
		Number	Per cent
"Light"	59	7	11.9
"Medium"	163	35	21.5
"Heavy"	180	61	33.9
Total	402	103	

Significant.

TABLE 4

Relationship of the Predominant Location of the Disease in the Homolateral Lung to Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained

HOMOLATERAL LUNG: PREDOMINANT LOCATION OF DISEASE	CASES	CONTRALATERAL REACTIVATION	
		Number	Per cent
Upper (2/3)	370	87	23.5
Lower (3/3)	118	25	21.2
Total	488	112	

Not significant.

Anatomic freedom from adhesions: After the collapse was well established and pneumonolysis, if any, had been completed, the films and fluoroscopic reports of each case were studied to determine the relative degree of freedom from adhesions between the lung and the chest wall, diaphragm and mediastinum. All cases classified as "poor anatomic collapse" ("poor" and "very poor") exhibited either extensive adhesions or adhesions of at least moderate degree adjacent to the principally involved area of lung. Those classified as "probably satisfactory collapse" ("fair", "good", and "excellent") included all which were adhesion free and others exhibiting moderate adhesions at some distance from the principally involved area or one or two stringlike adhesions confined to this area.

In table 5 is seen a marked reduction in the incidence of contralateral reactiva-

TABLE 5

Relationship of Anatomic Freedom from Adhesions to Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained: All Cases

TYPE OF COLLAPSE	CASES	CONTRALATERAL REACTIVATION	
		Number	Per cent
"Poor anatomic collapse"	335	118	35.2
"Probably satisfactory collapse"	222	17	7.7
Total	557	135	

Significant.

TABLE 6

Correlation of "Activity" of Disease in Contralateral Lung and Anatomic Freedom from Adhesions in the Homolateral Lung to the Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained

CONTRALATERAL: "ACTIVITY" OF DISEASE	HOMOLATERAL: TYPE OF COLLAPSE	CASES	CONTRALATERAL REACTIVATION		
			Number	Per cent	
None	"Poor"	98	18	18.4	Significant
	"Probably satisfactory"	74	3	4.1	
"Inactive"	"Poor"	54	5	9.3	Not significant
	"Probably satisfactory"	39	1	2.6	
"Active"	"Poor"	184	95	51.6	Significant
	"Probably satisfactory"	108	13	12.0	
Total		557	135		

TABLE 7

Relationship of Anatomic Freedom from Adhesions to Incidence of Contralateral Reactivation During the Time Pneumothorax Was Maintained: Cases Attaining Closure of Homolateral Cavities Within One Year After Induction Only

TYPE OF COLLAPSE	CASES	CONTRALATERAL REACTIVATION	
		Number	Per cent
"Poor anatomic collapse"	279	62	22.2
"Probably satisfactory collapse"	103	9	8.7
Total	382	71	

Significant.

tion among those cases with a "probably satisfactory" collapse. This finding is in agreement with two previous reports (2, 3) and at odds with another (1).

In table 6, the cases were subdivided according to both the "activity" of the contralateral disease and the anatomic freedom from adhesions of the col-

lapsed lung. When the contralateral disease was "active" or when that lung was roentgenographically clear, the degree of freedom from adhesions of the collapsed lung was found to be related to the incidence of subsequent contralateral reactivation. When the contralateral disease was "inactive" before induction, there was a similar difference but not to a significant degree.

Additional evidence in support of the findings of tables 5 and 6 is presented in table 7. Only cases which achieved cavity closure by the end of the first year are studied here. Eighty-two cases without cavity at the time of induction and 93 with open cavity at one year after induction are necessarily excluded. A strong relationship is again demonstrated between the degree of freedom from adhesions and the incidence of contralateral reactivation.

A possible relationship between contralateral reactivation and other factors, such as age of disease, dynamic status of disease, cavity size, and similar factors, was also sought. No such relationships could be demonstrated.

It is apparent that both selection (tables 1, 2, 3) and management (tables 5, 6, 7) of the average pneumothorax case have an important bearing upon later developments in the contralateral lung.

SUMMARY

The incidence of reactivation of disease in the contralateral lung during unilateral pneumothorax therapy was found to have a significant relationship to the following factors: the presence and activity (but not extent) of disease in the contralateral lung; the density of the roentgenographic shadows in the collapsed lung; and the anatomic freedom from adhesions of the collapsed lung.

The course of events in the contralateral lung should be given serious consideration in the evaluation of unilateral pneumothorax.

SUMARIO

Neumotórax Terapéutico. Análisis Estadístico de 557 Casos Iniciados en 1930–1939 y Reobservadas en 1949: II. El Destino del Pulmón Contralateral

La incidencia de la desintegración de la enfermedad en el pulmón contralateral durante la colapsoterapia unilateral mostró que guardaba relación significativa con los siguientes puntos: presencia y actividad (pero no extensión) de la enfermedad en el pulmón contralateral y densidad de las sombras roentgenográficas e inexistencia anatómica de adherencias del pulmón aplastado.

En la justipreciación del neumotórax unilateral, hay que prestar atención detenida a la evolución de los acontecimientos en el pulmón contralateral.

RESUME

Pneumothorax artificiel. Analyse statistique de 557 cas instaurés en 1930–1939 et réexaminés en 1949: II. Avenir du poumon opposé

La fréquence de l'amélioration observée dans le poumon opposé au cours de la collapsothérapie unilatérale a été trouvée en relation avec les conditions sui-

vantes: l'existence et l'activité (non l'étendue) de la tuberculose dans le poumon opposé, la densité des ombres sur les clichés radiographiques et l'absence de brides au niveau du poumon collabé.

Les phénomènes qui se produisent ultérieurement dans le poumon opposé doivent être pris en considération dans l'évaluation du pneumothorax unilatéral.

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ARTIFICIAL PNEUMOTHORAX: A STATISTICAL ANALYSIS OF 557 CASES INITIATED IN 1930–1939 AND FOLLOWED IN 1949[1,2]

III. The Influence of Features of Management After Induction on Early and Late Results

ROGER S. MITCHELL

(Received for publication March 30, 1951)

INTRODUCTION

The relationship of various *pre-induction* clinical features to early and late results in pulmonary tuberculosis treated with artificial pneumothorax has recently been reported (1). The present report is based upon the same 557 cases, which are now studied from the standpoint of the relative importance of various features of the *management* of pneumothorax *after* induction. A description of materials and methods, definitions of "good" and "poor" results, and the criteria of statistical significance used may be found in the first report of this series (1).

As in the preceding reports, attention is directed more to the relative than to the absolute value of the percentages presented in the present report. Some cases have again been excluded from certain of the tables because pertinent data were lacking.

RESULTS

Sudden airlessness and contraction of lung soon after induction: There is considerable evidence that sudden contraction and airlessness of a lobe or of the entire lung soon after pneumothorax induction is related to obstruction of major bronchi (2, 3). Accordingly, chest roentgenograms obtained within two months after induction of pneumothorax were reviewed in a search for such changes in this series.

The observation was made in only 24, 5.6 per cent of the cases. In spite of the fact that empyema was later found to be much more common in those with this finding (4), the over-all results were about the same as in those not exhibiting this phenomenon.

Anatomic freedom from adhesions: The type of collapse had a very close relationship to results (table 1). In this report, the type of collapse means the *degree of anatomic freedom* of the lung from the chest wall, diaphragm, and mediastinum. Each estimate was based upon reports of fluoroscopy and thoracoscopy and a review of serial single and stereoscopic chest roentgenograms taken during the first year after induction, and after pneumonolysis if performed.

Pneumonolysis was used in 26 per cent of this series; two or more such opera-

[1] From Trudeau Sanatorium, Trudeau, New York.

[2] Presented, in part, before the Medical Session, as part of the *Clinical Session* at the 47th annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1951.

tions were performed in 3 per cent of the group, and thoracoscopy without severance of adhesions was performed in only three instances. These operations include those performed before and after discharge, but only during the first year after induction of pneumothorax. Open pneumonolysis was not used.

A collapse was designated as "excellent" when there were no visible adhesions between the lung and chest wall, diaphragm, or mediastinum. In collapse designated as "good", there was an almost free pleural space, with no adhesions near the principally diseased area for which pneumothorax was given. In a "fair" collapse there was either a pleural space which was free except for a few small adhesions at, or quite near, the area under treatment, or when more extensive adhesions were present, well away from the principally diseased area.

TABLE 1

Relationship of Degree of Anatomic Freedom from Adhesions to Early and Late Results

TYPE OF COLLAPSE	CUMULATIVE "GOOD" RESULTS								
	At the end of the first year			At abandonment			At three years after abandonment		
	Evaluable cases	"Good"		Evaluable cases	"Good"		Evaluable cases	"Good"	
		Number	Per cent		Number	Per cent		Number	Per cent
"Very poor"	180	70	*38.9*	176	49	*27.8*	173	39	*22.5*
"Poor"	155	95	*61.3*	153	67	*43.8*	149	54	*36.2*
"Fair"	97	65	*67.0*	94	54	*57.4*	93	49	*52.7*
"Good"	49	35	*71.4*	47	28	*59.6*	47	26	*55.3*
"Excellent"	76	51	*67.1*	75	47	*62.6*	70	36	*51.4*
Total	557	316		545	245		532	204	
			Significant			Significant			Significant

"Poor" and "very poor" collapses represent two degrees of extensive interadherence, including broad adhesions to the principally involved portions of lung in each instance.

In short, "poor" and "very poor" collapses were, by modern standards, those in unquestioned need of pneumonolysis or abandonment; those with a "good" or "excellent" collapse were interpreted retrospectively by the writer as satisfactory; in those with a "fair" collapse, the need for pneumonolysis could not be clearly determined from the films or fluoroscopy and thoracoscopy reports.

Attention is directed to the unfavorable *late* results in cases with "poor" collapse. *Early* results in these cases had been deceptively as favorable as results observed in cases with greater anatomic freedom from adhesions.

Early cavity closure and sputum "conversion," the commonly used criteria of a so-called "effective" collapse, were *not* used in estimating type of collapse in this study. The importance of anatomic freedom from adhesions has been

emphasized (2, 5–11). Many other writers, however, either refer to a so-called "clinically effective" collapse without too clear a definition, or simply fail to distinguish between types of collapse in reporting their observations on pneumothorax. The considerable difference in results between these two methods of defining "effective" pneumothorax is made clear later in table 11.

Only 125 (22 per cent) of the 557 cases continued treatment with a "good" or "excellent" collapse. Furthermore, only 72 (11.1 per cent) had a collapse classified as "good" or "excellent" *before* pneumonolysis. This compares with 5 per cent (11), 8 per cent (8), and 10 per cent (12) of *spontaneous* freedom from adhesions previously reported.

TABLE 2

Relationship of the Severance of Adhesions to Results: All Cases with "Probably Satisfactory Collapse"

ALL CASES WITH "PROBABLY SATISFACTORY COLLAPSE"	EVALUABLE CASES	CLINICAL RESULTS STILL "GOOD" AT 3 YEARS AFTER ABANDONMENT	
		Number	Per cent
Without pneumonolysis	127	72	*56.7*
After pneumonolysis	83	39	*47.0*

Not significant

TABLE 3

Relationship of the Severance of Adhesions to Results: Selected Cases with "Probably Satisfactory Collapse"

"PROBABLY SATISFACTORY COLLAPSE"	EVALUABLE CASES	CLINICAL RESULTS STILL "GOOD" AT 3 YEARS AFTER ABANDONMENT	
		Number	Per cent
Without pneumonolysis	71	46	*64.8*
After pneumonolysis	31	19	*61.3*

Not significant

All cases with a "fair" collapse or better (i.e., "probably satisfactory") were divided into (a) those in which no pneumonolysis had been performed and (b) those in which a poor collapse had been converted from "poor" or "very poor" to "fair" or better by pneumonolysis. Late results in these two series are compared in table 2.

While the difference between these percentages was not large, there was virtually *no* difference when cases were well selected (1) for pneumothorax by the exclusion of those with "heavy"[3] roentgenographic shadows, preinduction roentgenographic evidence of endobronchial obstruction,[3] "old"[3] fibroid disease, and cavity in the contralateral lung (table 3).

The data in tables 2 and 3 indicate that, if a satisfactory anatomic collapse

[3] Defined in paper I of this series.

can be obtained by pneumonolysis, clinical results will parallel those observed when the satisfactory collapse occurs spontaneously, other factors being equal.

It is interesting that the gross location of the cavity or principal focus of disease under treatment bore a striking relationship to the type of collapse observed *before* pneumonolysis (table 4).

Adhesions at the area of principal involvement: The clinical importance of a few stringlike adhesions at the area of principal involvement, as distinguished from more extensive adhesions, is considered in tables 5 and 6. Since extensive adhesions were present in all cases classified as "poor" and "very poor" collapse,

TABLE 4

Relationship of Gross Location of Disease to the Extent of Adhesions Found After Induction

PREDOMINANT LOCATION OF DISEASE	TOTAL CASES	CASES WITH "PROBABLY SATISFACTORY COLLAPSE" BEFORE PNEUMONOLYSIS	
		Number	Per cent
Upper half	341	62	*18.2*
Lower half	126	68	*54.0*
Total	467		

Significant

TABLE 5

Relationship of Adhesions at the Area of Principal Involvement to Late Results: Cases with "Poor Anatomic Collapse" Excluded

ADHESIONS AT AREA OF PRINCIPAL INVOLVEMENT	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Absent	59	35	*59.3*
Present	131	72	*55.0*
Total	190	107	

Not significant

these cases were excluded in order to eliminate the factor of type of collapse in general (table 5). Possible weighting of the series was further reduced by exclusion from this group of those cases with "heavy" roentgenographic shadows, preinduction roentgenographic evidence of endobronchial obstruction, "old" fibroid disease, and cavity in the contralateral lung (table 6). Clinical results were somewhat better in the absence of adhesions at the area of principal involvement.

Upper mediastinal adhesions: The same two selected series of cases reported in tables 5 and 6 are again reported in tables 7 and 8. In the latter instances, however, the type of collapse is viewed from the standpoint of the presence or

absence of adhesions in the upper mediastinum. The numerical differences were greater than in the foregoing study and are large enough to merit consideration.

TABLE 6

Relationship of Adhesions at the Area of Principal Involvement to Late Results: Cases with Gross Contraindications to Pneumothorax and "Poor Anatomic Collapse" Excluded

ADHESIONS AT AREA OF PRINCIPAL INVOLVEMENT	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Absent	36	22	*61.1*
Present	63	33	*52.5*
Total	99	55	

Not significant

TABLE 7

Relationship of Adhesions in the Upper Mediastinum to Late Results: All Cases with "Poor Anatomic Collapse" Excluded

UPPER MEDIASTINAL ADHESIONS	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Absent	129	77	*59.7*
Present	61	30	*49.2*
Total	190	107	

Not significant

TABLE 8

Relationship of Adhesions in the Upper Mediastinum to Late Results: Cases with Gross Contraindications to Pneumothorax and "Poor Anatomic Collapse" Excluded

UPPER MEDIASTINAL ADHESIONS	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
Absent	55	36	*65.5*
Present	44	19	*43.2*
Total	99	55	

Not significant

The importance of upper mediastinal adhesions has previously been stressed (8, 13).

Type of pressure used: The use of positive-pressure pneumothorax was found

to be associated with a significantly higher incidence of clinical failure than when negative-pressure pneumothorax was utilized. The record of pressures observed while the patient received pneumothorax at the Sanatorium was the source of this determination. If, after the administration of air, pressures were positive on both inspiration and expiration with any consistency, the case was classified as receiving positive-pressure pneumothorax. Since all cases classified as receiving positive pressures were more apt to exhibit adhesions, the result is considered simply an amplification of the findings of table 2 on type of collapse. Positive-pressure pneumothorax has been previously reported as occasionally helpful (14), not harmful (15), and of no value (6, 16, 17).

Speed of cavity closure: "Cavity closure" was diagnosed when homolateral cavity could no longer be seen on serial single and stereoscopic roentgenograms. Reappearance of cavity within the first year led to classification as "open"; if cavity reappeared and again closed, closure was diagnosed as of the date of

TABLE 9

Relationship of Speed of Cavity Closure to Late Results

MONTHS TO CAVITY CLOSURE	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
1–4	214	122	*57.0*
5–8	82	43	*52.4*
9–12	20	5	*25.0*
Total	316	170	

Probably significant

final closure. Planigrams were not available during the time these cases were treated. The speed of cavity closure was found to have a relationship to results with pneumothorax when the first year after induction was divided into three four-month periods (table 9). When cases showing cavity closure within the first four months were further subdivided, similar differences were again present, but rather small. Necessarily excluded from this study were those cases with no cavity, those with cavity still open at the end of the first year, and those showing cavity closure within twelve months but in which the exact time of closure was unknown because of missing or inconclusive roentgenograms. Cavities slow in closing have been observed to reappear frequently at the time of abandonment (13).

Speed of sputum conversion: The speed of sputum conversion was found not to have an important relationship to late results (table 10). Sputum was classified as "negative" when two or more consecutive fifty-hour concentrated smears were found negative for acid-fast bacilli. Results of sputum cultures and gastric washing cultures are not included in this study since they were used only rarely and then only in the latter years of the study. Cases excluded from consideration

were those still positive for acid-fast bacilli after one year, those "negative" at one year but in which the approximate time of "conversion" not clearly established, and 6 cases with sputum repeatedly negative for acid-fast bacilli both before and after induction of pneumothorax.

Speed of combined cavity closure and sputum "conversion": The speed of attainment of "clinically effective" pneumothorax (cavity closure plus sputum "conversion") was found to have no relationship to late results when the factor of anatomic freedom from adhesions was eliminated (table 11).

TABLE 10

Relationship of Speed of Sputum Conversion to Late Results

MONTHS TO SPUTUM CONVERSION	EVALUABLE CASES	CUMULATIVE "GOOD" RESULTS AT THREE YEARS AFTER ABANDONMENT	
		Number	Per cent
1–4	136	85[NS]	*62.5*
5–8	87	49[NS]	*56.3*
9–12	55	29[NS]	*52.7*
Total	278	163	

Not significant

TABLE 11

Clinical Effectiveness vs. Type of Collapse: Their Relative Influence upon Late Results

CAVITY CLOSURE AND SPUTUM CONVERSION ATTAINED	"POOR ANATOMIC COLLAPSE"			"PROBABLY SATISFACTORY COLLAPSE"			
	Cases	"Good" results at three years after abandonment		Cases	"Good" results at three years after abandonment		
		Number	Per cent		Number	Per cent	
(months)							
1–6	104	53	*51.0*	85	65	*76.5*	Significant
7–12	43	20	*46.5*	50	37	*74.0*	Probably significant
Total	147	73		135	102		
		Not significant			Not significant		

Viewed differently, late results were very much better in the cases with "probably satisfactory collapse"[4] than in those with "poor anatomic collapse"[4] even though all cases considered had achieved "clinical effectiveness" within one year following induction.

Duration of "modified" bed rest after induction: "Modified" bed rest, as used in these patients, is defined as at least twenty to twenty-one hours per day in bed or reclining on a chaise longue; full bathroom privileges, meals in an adjoining room, and occasional necessary trips from one building to another were permitted.

[4] Defined in paper II of this series.

Time spent at bed rest immediately before and after discharge is included when it was consecutive with bed rest taken at Trudeau Sanatorium. No case was included in the study unless clinical progress was satisfactory up to the time of termination of bed rest. Exact duration of bed rest must have been known, and the case must have been followed for at least three years after abandonment.

In the 257 cases meeting these requirements, the mean duration of "modified" bed rest used was 6.2 months in cases with moderately advanced, and 9.7 months in those with far advanced, disease. These cases when so divided exhibited no evidence of a relationship between the duration of "modified" bed rest and late results. In addition, no relationship could be detected when total diameter of cavitation was used instead of the National Tuberculosis Association classification as the criterion of extent of disease. A relationship also was lacking when the dividing line between more and less "modified" bed rest was placed at 3, 5, 6, 8, or 9 months. Unfortunately, there were too few cases to permit a division into more than two variables of "modified" bed rest.

Myers has reported that more late deaths and reactivations occurred in 119 cases receiving more than three months of bed rest after pneumothorax than in 120 comparable cases receiving bed rest of three months or less (18).

Duration of sanatorium residence after induction: A study of the relationship of the duration of sanatorium residence to late results was made in the same manner as the foregoing study of "modified" bed rest. Time spent in other sanatoriums immediately before admission to, and after discharge from, Trudeau Sanatorium was included. All cases classified as "poor" results before discharge were excluded because in these cases the duration of sanatorium residence was often prolonged *because* of the poor result. When 9 months was used as the dividing line between a short and a long sanatorium stay, there was no demonstrable relationship between duration of sanatorium residence and late results with pneumothorax. The same lack of correlation was found when 4, 6, or 12 months were used as the dividing line. The mean duration of sanatorium residence was 10.6 months in those with moderately advanced, and 13.8 months in those with far advanced, disease.

Time away from full employment after induction: This analysis was carried out in the same manner as were the two preceding studies. Cases classified as "poor" results before return to full employment and those in which the time away from full employment could not be determined were excluded from consideration for similar reasons. When 24 months was used as the dividing line between a short and a long time away from full-time employment, no relationship could be demonstrated. When 12, 18, or 36 months were used as the dividing line between more and less time away from full employment, still no consistent relationship could be demonstrated. The mean time away from full employment was 32.9 months for those with moderately advanced, and 34.6 for those with far advanced, disease.

Duration of pneumothorax: In tables 12a and 12b, a study is made of the effect of duration of pneumothorax on late results. Cases lacking adequate pertinent data were excluded as in the three studies of rest. No case was

included unless still classified as a "good" result up to the time that abandonment was begun.

Pneumothorax may have been prolonged in certain instances because of clinical developments interpreted as reactivation of disease during the conduct of pneumothorax or at a trial of abandonment. Every effort was made to unearth all such information. A frank reactivation of disease coincident with a *trial* at abandonment was reported three times in this series; such cases were classified as reactivations at abandonment in spite of resumption of collapse.

TABLE 12

Relationship of Duration of Pneumothorax to Results with Pneumothorax Three Years After Abandonment: Cases "Poor" Before Abandonment Excluded

Duration of pneumothorax	a) Correlated with extent of disease as measured by the NTA classification					
	Moderately Advanced			Far Advanced		
	Evaluable cases	"Good" results		Evaluable cases	"Good" results	
		Number	Per cent		Number	Per cent
(months)						
6–36	58	45	*77.6*	26	21	*80.8*
36 or more	129	109	*84.5*	30	23	*76.8*
Total	187	154		56	44	
		Not significant			Not significant	

	b) Correlated with extent of disease as measured by cavity size								
	0.5 to 2.0 cm.			2.5 to 3.5 cm.			4.0+ cm.		
	Evaluable cases	"Good" results		Evaluable cases	"Good" results		Evaluable cases	"Good" results	
		Number	Per cent		Number	Per cent		Number	Per cent
6–36	44	39	*88.6*	19	16	*84.2*	8	5	*62.5*
37 or more	85	68	*80.0*	43	40	*93.0*	17	14	*82.4*
Total	129	107		62	56		25	19	
		Not significant			Not significant			Not significant	

The duration of pneumothorax to that point provided the figures used in tables 12a and 12b.

Regardless of whether extent of disease was measured by the NTA classification (table 12a) or by cavity size (table 12b), there was no tendency to use pneumothorax longer in cases with more extensive disease. In fact, of the 243 cases studied in table 12a, the mean duration of pneumothorax in the 187 cases with moderately advanced disease was 54.6 months, while it was only 46.9 months in the 56 with far advanced disease.

Using 36 months as the dividing line between a short and long duration of pneumothorax, this study revealed no correlation between this factor and late

results with pneumothorax. In addition, no correlation could be demonstrated when the dividing line between a short- and long-term pneumothorax was made at 24 or 48 months, nor when multiple subdivisions were used. These findings concur with some previous observations (19, 20, 21, 22); others have reported that results are better, the longer pneumothorax is continued (12, 23, 24).

The possibility of a relationship between any two of the factors considered in this and the first report (1) was also studied. Only one such relationship was found: location of disease was found to have a relationship to the severity of adhesions (table 5).

DISCUSSION

The degree of freedom from adhesions was found to be the most important factor in the management of pneumothorax. The accurate determination of this factor requires not only roentgenography, but also fluoroscopy and thoracoscopy. It is clear that the standard postero-anterior chest film may prove quite unreliable in some instances of apparent freedom of the lung from adhesions. While thoracoscopy was used in only about 26 per cent of this series, numerous fluoroscopic reports were available in every case.

The findings of tables 1, 5, 6, 7, and 8 may be interpreted as suggesting that freedom from adhesions need not be complete in order to obtain a satisfactory long-term clinical result. For example, cases with a "fair" collapse yielded late results as favorable as those with a "good" and "excellent" collapse (table 1). Moreover, small adhesions limited to the area of principal involvement (tables 5 and 6) and superior mediastinum (tables 7 and 8) could not be shown to have a statistically significant effect on results. On the other hand, there was a definite trend in favor of complete freedom from adhesions in both these studies. Furthermore, all tables may have been weighted by the inclusion of a considerable number of patients given pneumothorax before an adequate trial of bed rest alone. A number of such patients would doubtless have recovered without pneumothorax and probably did recover in spite of the type of collapse obtained. The over-all impression gained in making this study was that, when all factors are considered, a complete anatomic freedom from adhesions is a most worthwhile objective.

The observation that only 11 per cent of this series had an anatomically satisfactory collapse without benefit of pneumonolysis (table 2) also emphasizes the very frequent need for this surgical procedure.

As a result of these observations, it is believed that thoracoscopy and, if possible, pneumonolysis should be performed as soon as possible after induction. Abandonment and alternative forms of treatment may then be considered in those patients with an uncorrectably poor anatomic collapse.

It must be re-emphasized that "type of collapse" as defined herein did not in any way involve the factors of prompt cavity closure and sputum "conversion." The latter considerations are the time-honored criteria of an "effective" collapse. It is indicated in table 11 that late results with an "effective" collapse in this

sense were strongly influenced by the degree of anatomic freedom from adhesions. On the other hand, late results in cases with a "probably satisfactory collapse" were not improved by the earlier attainment of clinical "effectiveness."

In finding no statistically significant relationship between the results of pneumothorax on the one hand, and the duration of "modified" bed rest, sanatorium residence, and time away from full employment on the other, one is not justified in concluding that supplementary rest is unimportant in the management of pneumothorax or that ambulatory pneumothorax is necessarily adequate treatment. In the first place, more rest was doubtless given the sicker patients; the attempt to eliminate the factor of extent of disease will not eliminate this important clinical consideration. It was believed to be impossible to introduce into these statistical computations all the factors involved in the determination of the amount of rest used in the individual cases. When various factors which were found to exert a deleterious effect on results with pneumothorax were excluded and cases of comparable extent of disease were again studied, rest was found to have an increasing relationship to late results. The number of cases available for these more refined studies was unfortunately too small to justify their detailed presentation here. Some pertinent data are presented in the final section of this series (25). It should also be stressed that the beneficial effects of rest could not be measured statistically in those cases *classified* as having a "poor" initial result.

The study of the relationship of duration of pneumothorax to late results (table 12) was inconclusive for the same reasons as were the studies of rest. Because of the lack of adequate criteria for abandoning pneumothorax, the duration of successful pneumothoraces was presumed to have been largely determined by the whim of doctor or patient. Short-term pneumothorax could not be evaluated statistically because only a few cases were abandoned in less than eighteen months, and those almost entirely because of an obliterative pleuritis or the patient's wish rather than as a result of medical judgment. The figures do suggest, however, that a two- or three-year pneumothorax is as reliable in the long run as a four- to six-year collapse. Additional and more significant data stressing the importance of curtailing the duration of pneumothorax will be presented later (26).

SUMMARY

Two features of the management of pneumothorax after induction were found to have an important relationship to late results: anatomic freedom from adhesions and the speed of cavity closure.

Anatomic freedom from adhesions was found to have a much greater relationship to late results with pneumothorax than speed of combined cavity closure and sputum "conversion."

Results in cases with a satisfactory anatomic collapse were as favorable when the collapse was obtained artificially by pneumonolysis as when obtained spontaneously.

A pneumothorax space was significantly more apt to contain adhesions when the disease under treatment was located predominantly in the upper, rather than in the lower, lung field.

Late results with pneumothorax are apparently not closely related to the duration of pneumothorax treatment.

Studies of the relationship of late results with pneumothorax to various aspects of rest taken after induction were inconclusive.

SUMARIO

Neumotórax Terapéutico. Análisis Estadístico de 557 Casos Iniciados en 1930-1939 y Reobservados en 1949. III. Influjode las Características de la Asistencia después de La Inducción sobre los Resultados Tempranos y Tardíos

Dos características de las asistencia del neumotórax después de la inducción mostraron una importante relación con los resultados tardíos: inexistencia anatómica de adherencias y la velocidad del cierre de la caverna.

La ausencia anatómica de adherencias mostró una relación mucho mayor con los resultados tardíos del neumotórax que la velocidad combinada del cierre de las cavernas y del viraje del esputo.

En los casos con un colapso anatómico satisfactorio, los resultados fueron igualmente favorables cuando el colapso era obtenido artificialmente por neumonolisis o espontáneamente.

Un espacio neumotorácico era significativamente más susceptible de contener adherencias cuando la enfermedad en vías de tratamiento estaba localizada predominantemente en el campo pulmonar superior que cuando estaba en el campo inferior.

Los resultados tardíos del neumotórax no guardan aparentemente íntima relación con la duración de la colapsoterapia.

Los estudios de la relación de los resultados tardíos obtenidos con el neumotórax con varias fases del descanso tomado después de la inducción no fueron terminantes.

RESUME

Pneumothorax artificiel. Analyse statistique de 557 cas instaurés en 1930-1939 et réexaminés en 1949. III. Influence des caractéristiques du pneumothorax après son instauration sur les résultats immédiats ou tardifs

Il a été constaté que l'existence de deux caractéristiques, lorsque le pneumothorax est réalisé, ont une étroite corrélation aved les résultats éloignés, ce sont: l'absence de brides et la rapidité d'oblitération des cavernes.

Il a été constaté que l'absence de brides est en corrélation encore plus étroite avec les résultats éloignés du pneumothorax que la rapidité de l'oblitération des cavernes avec crachats négatifs.

Les résultats des cas où il existe un collapsus anatomique satisfaisant, sont aussi bons quand ce collapsus est obtenu artificiellement que lorsqu'il est spontané.

La présence de brides est beaucoup plus fréquente quand l'affection traitée intéresse plus particulièrement la zone apicale que le segment pulmonaire inférieur.

Les résultats éloignés du pneumothorax ne semblent pas étroitement liés à la durée du traitement.

Aucune conclusion n'a pu être tirée de l'étude des rapports enter les résultats éloignés du pneumothorax et les diverses modalités des cures de repos mises en oeuvre après la création d'un pneumothorax.

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THE MANAGEMENT OF MASSIVE TUBERCULOUS PNEUMONIA[1, 2]

A Therapeutic Review of Seventy-Five Cases

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INTRODUCTION

Massive tuberculous pneumonia is a serious condition, and prior to the use of streptomycin was generally considered to be a fatal disease. During the early days of the patient's illness tuberculous pneumonia is usually difficult to distinguish from other forms of bacterial pneumonia, and suspicion concerning its true nature may first be aroused by failure of the illness to subside despite therapy with penicillin or certain other antimicrobial drugs. Tissue destruction occurs early in tuberculous pneumonia, and large cavities often form, sometimes involving an entire lobe. Death may occur before this takes place, but usually the patient lives on for several months, continuing ill until death.

Treatment with streptomycin has usually been found effective in quickly reducing the toxicity and promoting clearing of the disease, as may be seen in the chest roentgenogram. It has been the general experience, however, that pulmonary cavities usually persist despite antimicrobial therapy, and the early addition of some form of collapse therapy is proved necessary for final attainment of a satisfactory result (1, 2).

In the present study of the treatment of massive tuberculous pneumonia, pneumoperitoneum was chosen as the particular form of collapse to be used in conjunction with the antimicrobial therapy. The choice of pneumoperitoneum was made because of its relative safety and in order to avoid the serious complications of spontaneous collapse, empyema, and unexpandable lung, which sometimes occur with artificial pneumothorax (3). Pneumoperitoneum was selected instead of the available thoracic surgical procedures because the former procedure could be applied to patients who were quite ill. Moreover, pneumoperitoneum had been found to be of value in the treatment of tuberculous pneumonia prior to the streptomycin era (4). Finally, pneumoperitoneum can easily be discontinued, does not prevent the later use of other collapse procedures, and may often be combined with them to good advantage.

This report is concerned with 75 patients with massive tuberculous pneumonia who were treated with streptomycin. Fifty-six of these patients also received pneumoperitoneum. The patients in the series were part of a large study of the effects of streptomycin on tuberculosis instituted by the Veterans Administration, the Army, and the Navy.

[1] From the Department of Medicine and Surgery, Veterans Administration, Oteen, North Carolina.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. Statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

PLAN OF STUDY

Criteria for diagnosis: The criteria employed for the diagnosis of massive tuberculous pneumonia consisted of: (*1*) the presence of large confluent dense shadows in the chest roentgenogram, involving one (but usually more than one) lobe of the lung; (*2*) high elevation of temperature and severe toxicity; (*3*) physical signs indicative of the presence of consolidation in most cases; and (*4*) tubercle bacilli in the sputum.

As a rule, it was possible to determine by earlier films that the pneumonic component was, at most, of only a few weeks' duration. In a few cases this could be determined only by the history. The two illustrative cases are repre-

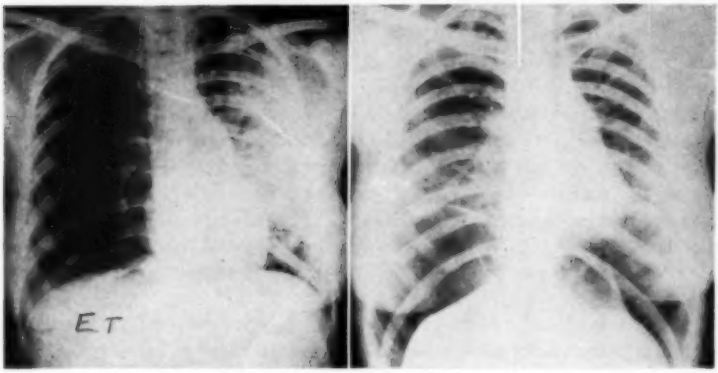

FIG. 1 (Left) White female, age 25. Chest roentgenogram, March 25, 1948, reveals massive tuberculous pneumonia in the left lung. Patient acutely ill, temperature 104°F. Streptomycin, April 1, 1948, 1.0 gm. daily for 42 days, plus pneumoperitoneum.

(Right) Chest roentgenogram, August 9, 1950, reveals complete clearing of pneumonic lesion. Sputum persistently negative for tubercle bacilli on concentrate and culture. Pneumoperitoneum continued. Patient discharged with disease arrested.

sentative of the average rather than of either the most or least severe degrees of involvement observed in the entire series.

Factors determining decision to induce pneumoperitoneum: The use of pneumoperitoneum and the timing of its introduction were influenced by several factors. In the early part of the study it was agreed that collapse therapy should be withheld to permit the evaluation of the effects of streptomycin alone. For this reason pneumoperitoneum was withheld in 16 patients. Pneumoperitoneum was refused by 3 additional patients. As may be seen in table 1, pneumoperitoneum was already in effect in 9 patients before the advent of the tuberculous pneumonia. In the remainder of those who received pneumoperitoneum, the time of induction was determined by trial and error in the first few patients treated. It was soon evident, however, that the occasional development of increased consolidation occurred when pneumoperitoneum and streptomycin were started

simultaneously. Further observation revealed that this consolidation could be avoided by delaying the induction of pneumoperitoneum for six to eight weeks, as defervescence of symptoms, a halting of the onward progress of the lesion, and the onset of roentgenographic clearing generally occurred within that time. This has also been observed by others (5). A general plan was therefore evolved

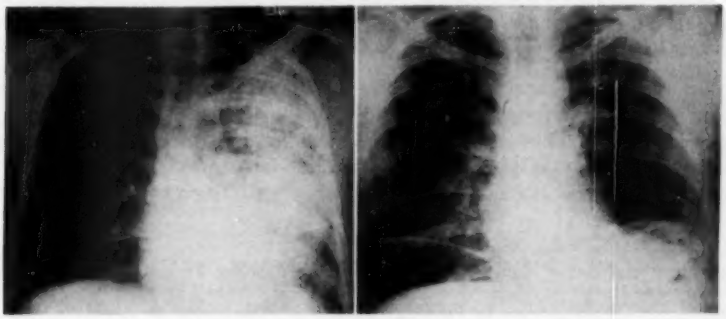

FIG. 2. (Left) Negro male, age 21. Chest roentgenogram, December 18, 1946, reveals massive tuberculous pneumonia in the left lung. Patient acutely ill, temperature 103°F. Streptomycin, December 24, 1946, 1.8 gm. daily for 120 days. No collapse therapy. Disease reactivated and pneumoperitoneum instituted.

(Right) Chest roentgenogram, May 17, 1949, reveals complete clearing of pneumonic lesion. Sputum persistently negative for tubercle bacilli on concentrate and culture. Pneumoperitoneum continued. Patient discharged as an arrested case. An excellent result has been attained, but it is believed that the failure to combine pneumoperitoneum with streptomycin early in the course of treatment permitted a reactivation of the disease.

TABLE 1

Relation of Time of Institution of Pneumoperitoneum with Streptomycin Treatment (56 Cases)

	MONTHS AFTER START OF STREPTOMYCIN							
	Before	0-1	1-2	2-3	3-4	4-5	5-6	6 Plus
Number	9	14	18	11	1	1	0	2
Per cent	16	25	32	19	2	2	0	4

Numbers refer to numbers of patients; percentages are derived from total receiving pneumoperitoneum.

to defer the pneumoperitoneum for this period of time after the beginning of streptomycin treatment.

Evaluation of roentgenograms: Roentgenographic changes at the end of streptomycin treatment, as shown in table 3, were evaluated on the basis of condensing all possible degrees of improvement and worsening into a seven-point scale. For example, "marked improvement" indicated that complete or very nearly complete clearing of the pulmonary lesion

had occurred. All films were interpreted by the same individual. Sputum "conversion" in all instances indicated that tubercle bacilli could not be found on concentrated smear or culture for at least three months.

Streptomycin regimens: Since an investigation of several streptomycin regimens in the treatment of pulmonary tuberculosis was under way, the dosage and duration of streptomycin therapy varied in the cases of this series. Ten patients received 1.8 gm. or 2.0 gm. of streptomycin daily for 120 days; 40 received 1.0 gm. daily for 42 days; 17 received 1.0 gm. every third day for 120 days; and 8 received 1.0 gm. of dihydrostreptomycin twice daily every third day for 120 days. No attempt was made to evaluate the results according to regimens because of the small number of cases.

Composition of clinical series: In table 2 it may be seen that most of the patients were in a young age group, particularly the decade from 20 to 30 years of age. Since white males were admitted to the hospital three times more commonly than Negro males, the proportion of the latter was less striking than it would have been if the admissions had been equal. There were relatively few

TABLE 2

Age, Race, and Sex of Seventy-Five Patients with Massive Tuberculous Pneumonia

AGE	20–25	26–30	31–40	41–50	51–60	TOTAL
White male	11	6	5	2	3	27
Negro male	19	11	8	1	6	45
White female	2	1	0	0	0	3
Negro female	0	0	0	0	0	0
Total	32	18	13	3	9	75

admissions of white females and almost none of Negro females, which made the proportion in these groups meaningless.

OBSERVATIONS

When the whole course of the disease was considered, it was found that the patients who received pneumoperitoneum attained better ultimate results than those not receiving it; but this difference was not apparent at the end of the streptomycin treatment. For this reason, the cases were not separated in accordance with the presence or absence of collapse therapy at that time.

Roentgenographic evaluation: As may be seen in table 3, at the end of streptomycin therapy a gratifying proportion (36 per cent) of the patients achieved marked improvement, with complete or almost complete clearing of the shadows observed in the roentgenograms, and an essentially equal proportion (35 per cent) achieved at least moderate roentgenographic clearing. Moreover, unfavorable progression of any degree occurred in only 5 per cent of the group. Such a low incidence of progression in so serious a condition as massive tuberculous pneumonia is evidence that a profound effect was exerted on the course of the disease.

The "conversion" of the sputum in only 21 per cent of the cases at the end of streptomycin therapy, as may be seen in table 4, was not too unsatisfactory

since the total period of therapy in most instances was only slightly longer than the period necessary to attain the designation "conversion," i.e., absence of tubercle bacilli for three or more months.

TABLE 3

Results According to Roentgenographic Evaluation at End of Streptomycin Treatment

ROENTGENOGRAPHIC CHANGES	NUMBER	PER CENT
Marked improvement	27	36
Moderate improvement	26	35
Slight improvement	9	12
Unchanged	9	12
Slight worsening	1	1
Moderate worsening	1	1
Marked worsening	2	3

TABLE 4

Results According to Sputum "Conversion" at End of Streptomycin Treatment

	NUMBER	PER CENT
Sputum "converted"	16	21
Not "converted"	59	79

TABLE 5

Roentgenographic and Bacteriologic Status in Successive Periods of Time

	MONTHS											
	0-6		7-12		13-18		19-24		25-30		31-36	
Roentgenographic evaluation	Improved	Worse	Improved	Worse	Improved	Worse	Improved	Worse	Improved	Worse	Improved	Worse
No collapse	11	9	8	6	5	4	4	2	1	0	1	0
Pneumoperitoneum	43	11	29	8	17	4	5	0	1	0	1	0
Pneumoperitoneum plus thoracoplasty	1	0	4	1	3	1	1	1	0	0	0	0
Tubercle bacilli in sputum	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**
No collapse	8	12	6	8	5	4	3	3	1	0	1	0
Pneumoperitoneum	22	32	22	15	16	5	5	0	1	0	1	0
Pneumoperitoneum plus thoracoplasty	0	1	2	3	1	3	0	2	0	0	0	0

Numbers refer to numbers of patients.

Role of pneumoperitoneum in total result: The course of the disease after the brief period of antimicrobial effect had passed was of more importance in evalu-

ating the real effectiveness of treatment, and it was in this period that the usefulness of pneumoperitoneum began to appear. In table 5 it should be noted that the figures express the status of only those patients available for observation in any one time segment and are not cumulative from one segment to another. The advantage of pneumoperitoneum appeared definite in so far as maintenance of continued roentgenographic improvement was concerned since approximately 4 of 5 patients with pneumoperitoneum achieved this state, whereas only slightly more than one-half did so without pneumoperitoneum. While no difference was seen in the proportion of patients achieving sputum negative for tubercle bacilli in the first six months, the evidence in favor of pneumoperitoneum increased with time, becoming apparent twelve to eighteen months after the start of therapy. By this time approximately three-fourths of

TABLE 6

Seventy-Five Patients with Massive Tuberculous Pneumonia
Status of Cases During Segments of Follow-Up

	MONTHS OF FOLLOW-UP					
	0-6	7-12	13-18	19-24	25-30	31-36
Still in hospital, improved	50	36	15	4	0	0
Still in hospital, unimproved	10	10	7	3	0	0
Ama,* not readmitted	6	5	6	1	0	0
Ama, readmitted, improved	0	0	0	1	1	0
Ama, readmitted, worse	0	0	0	0	0	0
Discharged arrested, not readmitted	0	1	5	5	1	2
Discharged arrested, readmitted	0	0	0	0	0	0
Transferred	1	1	0	0	0	0
Dead	8	4	2	0	0	0
Totals	75	57	35	14	2	2

* Discharged against medical advice.

the patients with pneumoperitoneum had "converted" their sputum, and only slightly more than one-half had done so without collapse therapy.

Unfortunately, the addition of thoracoplasty following pneumoperitoneum did not increase incidence of sputum "conversion" in the 7 cases in which this was tried. For completeness it should be stated that 5 of the patients listed as receiving no collapse therapy received phrenemphraxis, 3 of whom refused the addition of pneumoperitoneum. Also one patient received a thoracoplasty in the seven- to twelve-month period following bed rest and streptomycin, and one other underwent a pulmonary resection in the thirteen- to eighteen-month period. Both of these attained roentgenographic improvement and sputum negative for tubercle bacilli.

Follow-up observations: In considering the condition of the patients in the follow-up period, the figures in table 6 express the status of only those patients available for observation in any one time segment and are not cumulative from

one segment to another. It was surprising that only 2 of the patients, both of whom had left the hospital against medical advice, were readmitted later and both had improved in the meantime. Moreover, it was encouraging to note that none of the 14 patients discharged with a classification of "arrested" had been readmitted and, in so far as it is known, none had relapsed. A total of 14 patients had died by the time of this report, and all deaths were due to tuberculosis. Ten deaths occurred among the 45 Negro males (22 per cent) and 4 among 27 white males (15 per cent). On the other hand, 6 (22 per cent) of the white males and 8 (18 per cent) of the Negro males had attained an arrest of their disease. While the number of patients was small, the results tend to support the clinical impression that the prognosis of this condition is less favorable in Negroes.

DISCUSSION

When the clinical experience with massive tuberculous pneumonia in the pre-streptomycin era is compared with the observations in streptomycin-treated patients such as those in the present series, it may be categorically stated that streptomycin is essential in the management of this condition. Moreover, because of the rapidly progressive nature of the disease, chemotherapy should be started as soon as possible (6).

Experience with additional patients treated more recently and not included in the present series has revealed that combined therapy, using streptomycin and para-aminosalicylic acid, may well be more effective than streptomycin alone since this combination has been found to delay the emergence of streptomycin-resistant organisms. It is also thought, at present, that almost all cases should receive at least four months' treatment and that moderately severe cases, such as those shown in figures 1 and 2, should have the combined therapy continued for eight to twelve months if the maximal expected clearing of roentgenographic shadows has not occurred.

It is believed from the observations reported that pneumoperitoneum should be used in all cases when feasible and it should be instituted within six to eight weeks after beginning antimicrobial therapy. In this way, the collapse therapy is not started until some regression of toxicity and roentgenographic improvement has occurred, and the increased consolidation sometimes seen when pneumoperitoneum and streptomycin are begun simultaneously may be avoided.

The effect of the addition of phrenemphraxis to pneumoperitoneum was not analyzed in the tables because individual characteristics of the disease so affected the indications for the procedure that the cases would have to be divided into too many small groups. It is believed, however, that the addition of phrenemphraxis is rarely, if ever, indicated in the early weeks of treatment. It may be added later after the pneumoperitoneum has been instituted, and it has proved particularly useful in cases of unilateral disease when the expected clearing of the lesion and disappearance of cavity have not been attained. In the present series, phrenemphraxis was added to the pneumoperitoneum in 11 patients at some time during their course of streptomycin therapy.

It is not intended to give the impression that pneumoperitoneum is the only form of collapse therapy needed in the over-all treatment of massive tuberculous pneumonia since it is evident from table 5 that several patients were subjected to thoracoplasty following its use. It is believed, however, that pneumoperitoneum aided these patients to reach a state in which an additional measure could be applied, and it is also evident that pneumoperitoneum alone served as a definitive form of collapse for many others.

SUMMARY

The results of the treatment of 75 cases of massive tuberculous pneumonia have been presented. All patients received streptomycin and 56 also received pneumoperitoneum. The members of the group have been followed from six months to three years after cessation of antimicrobial therapy.

It has been concluded that the use of streptomycin is necessary in all cases of massive tuberculous pneumonia and that treatment should be begun as soon as possible. The addition of pneumoperitoneum early in the course of streptomycin therapy, in most cases, greatly improved the final result of treatment.

SUMARIO

La Asistencia de la Neumonía Tuberculosa Masiva: Repaso Terapéutico de Setenta y Cinco Casos

Preséntase aquí el resultado del tratamiento de 75 casos de neumonía tuberculosa masiva. Todos los enfermos recibieron estreptomicina y 56 además el neumoperitoneo, habiendo sido los mismos mantenidos en observación de seis meses a tres años después del cese de la antibioticoterapia.

Dedúcese que el empleo de la estreptomicina es necesario en todos los casos de neumonía tuberculosa masiva y que el tratamiento debe comenzar cuanto antes. La adición del neumoperitoneo al principio de la estreptomicinoterapia mejoró considerablemente el resultado final de la terapéutica.

RESUME

Traitement de la pneumonie tuberculeuse massive—Revue de la thérapeutique dans soixante-quinze cas

Les résultats du traitement dans 75 cas de pneumonie tuberculeuse avec infiltration massive sont présentés. Tous les malades ont reçu de la streptomycine avec adjonction d'un pneumopéritoine chez 56 d'entre eux. Après cessation de la thérapie antibiotique ces malades ont été suivis pendant une période de six mois à trois ans.

La conclusion est que l'emploi de la streptomycine est nécessaire dans tous les cas de pneumonie tuberculeuse massive et que ce traitement doit être instauré aussitôt que possible. L'adjonction précoce du pneumopéritoine au cours de la streptomycinothérapie a, dans la plupart des cas, amélioré considérablement le résultat final du traitement.

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ELECTROCARDIOGRAPHIC CHANGES ACCOMPANYING PULMONARY COLLAPSE THERAPY AND THORACIC SURGERY[1,2]

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In recent years the increased use of pulmonary collapse therapy and thoracic surgical procedures has produced special problems of electrocardiographic interpretation, because of the accompanying changes in the position of the heart within the thorax. The purpose of this study is to describe the electrocardiographic changes resulting from these procedures and to attempt to correlate these changes with roentgenographically observed changes in heart position.

PLAN OF INVESTIGATION

In most cases, 12 or 13 lead electrocardiograms were taken before and after the procedures being studied. The leads employed were: I, II, III, aV_R, aV_L, aV_F, V_{CR}, and V_1 through V_6. In a few cases only leads I, II, III, V_2, V_4, and V_5 were available.

Leads I, II, and III are the standard limb leads and are self-explanatory. The precordial leads, or V leads, were taken with one electrode over the precordium and the other electrode (indifferent electrode of Wilson) simultaneously connected to all three extremities, there being a resistor of 5,000 to 10,000 ohms interposed between this electrode and each of the extremities. The position of the precordial electrode is indicated by the number in the designation of the lead as follows: V_1: the precordial electrode is in the fourth interspace at the right edge of the sternum; V_2: the precordial electrode is in the fourth interspace at the left edge of the sternum; V_3: the precordial electrode is midway between positions of V_2 and V_4; V_5: the precordial electrode is in the fifth interspace in the left mid-clavicular line; V_5: the precordial electrode is in the left anterior axillary line at the level of lead V_4; V_6: the precordial electrode is in the left mid-axillary line at the level of lead V_4; V_{CR}: the precordial electrode is in the fifth interspace in the right mid-clavicular line. Leads aV_R, aV_L, and aV_F have been called "Goldberger" leads or augmented "unipolar" extremity leads. These are not true unipolar leads, since they actually measure the difference in potential between two electrodes, one (the indifferent electrode) being placed at a great distance from the heart (in this instance an electrode connected to all three extremities, each through resistors of 5,000 to 10,000 ohms); and the other being placed on the extremity for which the lead is named: right arm, aV_R; left arm, aV_L; left leg, aV_F. The amplitude of the deflections in these leads is augmented by a method, described by Goldberger, of disconnecting one of the appropriate leads which make up the indifferent electrode.

The "electrocardiographic" or "electrical" position of the heart was described using the criteria of Wilson (1). *Vertical position:* the ventricular complexes of lead aV_L resemble those of leads V_1 and V_2. The ventricular complexes of lead aV_F resemble those of leads V_5 and

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TABLE 1

Tabulation of Electrocardiographic Changes

PATIENT	PROCEDURE	SIDE	"ELECTRICAL POSITION" BEFORE PROCEDURE	POSITIONAL CHANGE	ANTERIOR TRANSITION ZONE SHIFT	QRS AMPLITUDE
C. S.	Pneumothorax	Right	Vertical	More vertical	To the left	Unchanged
H. M.	Pneumothorax	Right	Semi-vertical	More vertical	To the left	Unchanged
M. T.	Pneumothorax	Right	Semi-vertical	More vertical	To the right	Unchanged
L. R.	Pneumothorax	Right	Intermediate	More horizontal	To the left	Unchanged
L. W.	Pneumothorax	Right	Intermediate	Unchanged	Unchanged	Unchanged
P. C.	Pneumothorax	Right	Vertical	More horizontal	To the right	Unchanged
G. D.	Pneumothorax	Right	Vertical	Unchanged	Unchanged	Unchanged
B. Z.	Pneumothorax	Right	Vertical	Unchanged	To the left	Smaller
V. O.	Pneumothorax	Right	Intermediate	More vertical	To the left	Smaller
H. W.	Pneumonectomy 5 months previously	Right	Vertical	More horizontal	To the right	Unchanged
F. K.	Pneumonectomy 1 week previously	Right	Vertical	More horizontal	To the left	Smaller
R. F.	Pneumonectomy 9 months previously	Right	Vertical	More horizontal	To the right	Unchanged
M. G.	Lobectomy 5 months previously	Right upper	Vertical	More horizontal	To the right	Unchanged
G. N.	Pneumonectomy 6 months previously	Right	Vertical	Unchanged	To the right	Unchanged
M. L.	Pneumonectomy 2 weeks previously	Right	Intermediate	More horizontal	To the left	Unchanged
M. M.	Lobectomy 2 weeks previously	Right lower	Intermediate	More horizontal	To the left	Unchanged
R. C.	Lobectomy 4 months previously	Right upper	Semi-vertical	More horizontal	To the right	Unchanged
S. B.	Thoracoplasty	Right	Semi-vertical	More horizontal	To the left	Unchanged
L. L.	Thoracoplasty	Right	Vertical	More horizontal	To the left	Unchanged
E. K.	Thoracoplasty	Right	Intermediate	More horizontal	To the left	Unchanged
M. E.	Thoracoplasty	Right	Semi-vertical	More horizontal	To the left	Unchanged
E. N.	Thoracoplasty	Right	Intermediate	Unchanged	Unchanged	Unchanged
L. I.	Pneumoperitoneum		Vertical	Unchanged	To the right	Unchanged
A. F.	Pneumoperitoneum		Vertical	More horizontal	To the right	Unchanged
T. T.	Pneumoperitoneum		Semi-vertical	More horizontal	To the right	Unchanged
M. V.	Pneumoperitoneum		Semi-horizontal	More horizontal	To the right	Unchanged
C. L.	Pneumoperitoneum		Semi-horizontal	More horizontal	To the right	Unchanged
J. V.	Pneumothorax	Left	Vertical	Unchanged	Unchanged	Smaller
A. S.	Pneumothorax	Left	Vertical	Unchanged	Unchanged	Smaller
M. S.	Pneumothorax	Left	Vertical	Unchanged	Unchanged	Smaller
J. C.	Pneumothorax	Left	Semi-horizontal	More vertical	Unchanged	Smaller
L. T.	Pneumothorax	Left	Intermediate	More vertical	To the left	Smaller
K. H.	Pneumothorax	Left	Semi-vertical	Unchanged	Unchanged	Smaller
D. S.	Pneumothorax	Left	Semi-vertical	Unchanged	Unchanged	Smaller
L. F.	Pneumothorax	Left	Semi-vertical	Unchanged	To the right	Smaller
S. T.	Pneumothorax	Left	Vertical	Unchanged	Unchanged	Smaller
I. S.	Pneumothorax	Left	Vertical	Unchanged	Unchanged	Smaller
S. A.	Thoracoplasty	Left	Vertical	More horizontal	Unchanged	Unchanged
J. F.	Thoracoplasty	Left	Intermediate	More horizontal	To the left	Unchanged
E. K.	Pneumonectomy	Left	Semi-vertical	More horizontal	To the left	Smaller
H. S.	Pneumonectomy	Left	Intermediate	Unchanged	To the left	Unchanged
E. S.	Pneumonectomy	Left	Vertical	More horizontal	To the left	Smaller
P. M.	Pneumonectomy	Left	Vertical	More horizontal	To the right	Increased
P. W.	Pneumonectomy	Left	Vertical	More horizontal	To the right	Smaller
L. H.	Pneumonectomy	Left	Intermediate	More horizontal	Unchanged	Smaller

None of the cases of pneumonectomy or lobectomy were preceded by collapse therapy except for patient F. K. who had a right pneumothorax for four years preceding right pneumonectomy.

V_6. *Semivertical position:* The ventricular complexes of lead aV_F resemble the ventricular complexes of leads V_5 and V_6. The ventricular complexes of lead aV_L are small. *Intermediate position:* The ventricular complexes of leads aV_L and aV_F are similar in form and size and are like those of leads V_5 and V_6. *Semihorizontal position:* the ventricular complexes of lead aV_L resemble those of leads V_5 and V_6. The ventricular complexes of lead aV_F are small. *Horizontal position:* the ventricular complexes of lead aV_L resemble those of leads V_5 and V_6. The ventricular complexes of lead aV_F resemble those of leads V_1 and V_2. *Indeterminate position:* there is no obvious relationship between the ventricular complexes of the limb leads and those of the precordial leads.

The transition zone of the QRS complex in the precordial leads is that region where the complexes assume an intermediate form between the right- and left-sided forms. In this study the transitional zone was arbitrarily considered to be present between those leads where the R/S ratio progressed from less than one to one or more than one.

The electrocardiographic changes in the 45 cases studied are tabulated in table 1. In each instance the amplitudes of all deflections were measured. A special ratio was derived from the ratios of R/S in aV_F and R/S in aV_L, viz., $\frac{\text{R/S in } aV_F}{\text{R/S in } aV_L}$. This ratio was used only to evaluate more quantitatively changes in electrical position, and has no absolute significance.

OBSERVATIONS

Right Pneumothorax

"Electrical" position: In 4 cases the "electrical" position became distinctly more vertical. This was evidenced by an increase in amplitude of the R-wave in aV_F and a decrease in the amplitude of the R-wave and/or an increase in the depth of the S-wave in aV_L. This was reflected in the standard limb leads by a decrease in amplitude of R_1 or the appearance of an S_1 and an increase in the amplitude of R_3. In three instances there was no change in the "electrical" position.

P-waves: In the 4 cases in which the heart became more vertical, the P-waves in lead I became smaller in three instances and inverted in the other instances. In each instance the P-waves became more inverted in lead aV_L and taller in lead aV_F and in leads II and III.

Transition zone of QRS complex in the chest leads: The transition zone was shifted to the left in 5 cases, slightly to the right in 2 cases, and remained unchanged in the remaining 2 cases.

T-waves: There was a decrease in amplitude of the T-waves in the right-sided chest leads (V_{4R}, V_1, and V_2) and an increase in amplitude in the left-sided leads (V_4, V_5, and V_6).

Right Pneumonectomy; Right Upper, Middle, or Lower Lobe Lobectomy

"Electrical" position: The "electrical" position became more horizontal in 7 of 8 cases and remained unchanged in the other. This was reflected in the standard limb leads by an increase in amplitude of R_1 and a decrease in R_3 and/or the appearance of an increase in the amplitude of S_3. The R/S ratio of aV_F/aV_L decreased in these cases.

P-waves: In most instances the P-waves became taller in aV_L. No other consistent change was noted.

Transition zone of QRS in the chest leads: In 5 cases the transition zone of QRS was shifted to the right, and in 3 cases to the left. In the 3 cases where the transition zone was shifted to the left, the electrocardiograms were obtained within two weeks after surgery, and in those cases roentgenograms revealed a shift of the mediastinum to the left.

T-waves: T-wave changes commensurate with QRS changes occurred in all instances (secondary T-wave changes of Bayley (2)).

Right thoracoplasty: "Electrical" position: The "electrical" position became more horizontal, but the degree of change was less marked than after right pneumonectomy.

P-waves: No consistent P-wave changes were noted.

Transition zone of QRS in the chest leads: The transition zone was always shifted to the left.

T-waves: T-wave changes commensurate with QRS changes occurred in every case.

Pneumoperitoneum

"Electrical" position: "Electrical" position of the heart always became more horizontal; R_1 became taller; and R_3, smaller; S_3 appeared or became deeper.

P-waves: No consistent P-wave changes were noted.

Transition zone of QRS in the chest leads: The transition zone was always shifted to the right.

T-waves: T-wave changes commensurate with QRS changes occurred in all instances.

Left Pneumothorax

"Electrical" position: In most instances there was no change in the "electrical" position, but in a few cases there was a shift to the vertical position.

P-waves: The P-waves became smaller in amplitude in all leads.

Transition zone of QRS in the chest leads: The transition zone did not change. There was a decrease in amplitude of QRS in all chest leads.

T-wave changes: The amplitude of the T-waves also decreased in all chest leads.

Left Pneumonectomy

"Electrical" position: The "electrical" position of the heart became more horizontal in all cases.

P-waves: The P-waves became taller in lead I, and taller or upright where previously inverted in aV_L.

Transition zone of QRS in the chest leads: The transition zone was shifted to the left and became much more sharply defined.

T-waves: T-wave changes were commensurate with QRS changes in all cases.

Left Thoracoplasty

"Electrical" position: The "electrical" position almost always tended to become more horizontal, although not to the same extent as after pneumonectomy.

P-waves: No P-wave changes were noted.

Transition zone of QRS in the chest leads: The transition zone was shifted to the left in one case; no changes were observed in the other case.

T-waves: T-wave variations were commensurate with QRS changes in all instances.

DISCUSSION

Since the more frequent use of collapse therapy and thoracic surgical procedures, many studies have appeared describing changes in electrocardiographic contour after these procedures. One of the early reported changes was the development of inversion of the T-waves in the CF leads (3). Recent studies (4) indicate that such changes are due to the influence of the left-leg electrode since they do not appear in V chest leads. Other studies that have appeared have been limited in their usefulness because of the limited number of leads utilized (5–17).

In general, after right pneumothorax the "electrical" position of the heart became more vertical. Some shift of the transition zone to the left was seen in the chest leads of the electrocardiogram. In left pneumothorax, similar changes occurred except that there was negligible shift of the transition zone. This is readily explainable by the roentgenographic observation that there is a shift of the mediastinum to the left in right pneumothorax, with the reverse occurring in left pneumothorax (figure 1). While some clockwise rotation undoubtedly exists in both instances, the opposite shifts in the position of the mediastinum either exaggerate or minimize the tendency for the transition zone to be shifted to the left. Further evidence that the heart has become more vertical is seen in the tendency for P in leads aV_L and I to become flatter or even inverted and to become taller in lead aV_F and lead III (figures 2A and B, and 3). This may be a result of rotation of the heart about its transverse axis (apex forward or apex backward); however, the criteria for such rotation are as yet poorly understood.

In left pneumothorax it was also noted that the amplitude of the QRS deflection in the precordial leads was diminished. This can be easily understood in view of the work of Katz and Robinow (18) on the effect of the interposition of a poor conductor between the heart and the site at which the electrode was applied (chest wall). In left pneumothorax there is an increased amount of air between the heart and the anterior chest wall, probably because the heart becomes displaced posteriorly when the patient is in the supine position. An extreme example showing such changes may be seen in a patient with a markedly fibrotic and contracted left lung in whom it was seen that a marked decrease in amplitude of QRS complexes in the chest leads was associated with marked posterior displacement of the heart (figure 4). As a matter of fact, the amplitude of QRS was tallest in leads taken posteriorly in the mid-scapular line (as was the intensity of the heart sounds).

After either right or left pneumonectomy, the essential electrocardiographic changes indicated that the "electrical" position of the heart had become more horizontal (figures 2C and D, and 5). This undoubtedly resulted, in great part, from the ipsilateral phrenico-exeresis with its accompanying diaphragmatic paralysis and elevation (figure 5). The change in the anatomic position of the heart is not necessarily the same after right as after left pneumonectomy, however, since a similar "electrical" position may actually reflect different degrees and directions of rotation of the heart. After left pneumonectomy, because of the marked elevation of the heart, it is probable that comparable lead positions would be as much as an interspace above the conventional positions, e.g., V_4 would be

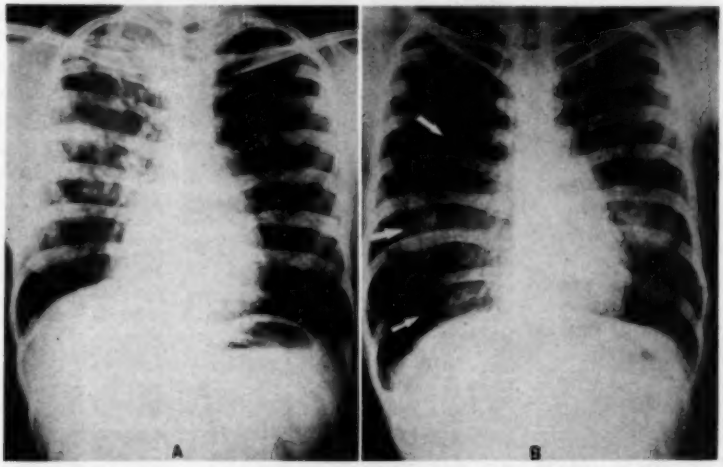

FIG. 1. Roentgenograms showing the heart becoming more vertical and the mediastinum shifted to the left after an artificially induced right pneumothorax. A is control film; B was obtained after right pneumothorax had been instituted. Note edge of lung in B (arrows).

in the mid-clavicular line in the fourth rather than in the fifth intercostal space. It was noted further that the position of the transition zone depended largely on the position of the mediastinum, which in turn varied with the interval following surgery. In the period immediately after surgery, there was usually a shift of the mediastinum to the unoperated side due to exudate and air. After several months the mediastinum became deviated toward the operated side (figure 6). The shift in the transition zone in the chest leads reflected these changes closely. A shift of the transition zone to the left may not only be reflected in the usual QRS changes, but also by inversion of the T-waves in V_2 and V_3 in some cases. This must be recognized and differentiated from the patterns of chronic coronary arterial insufficiency.

It is important to realize that in cases where extensive extirpative or collapse

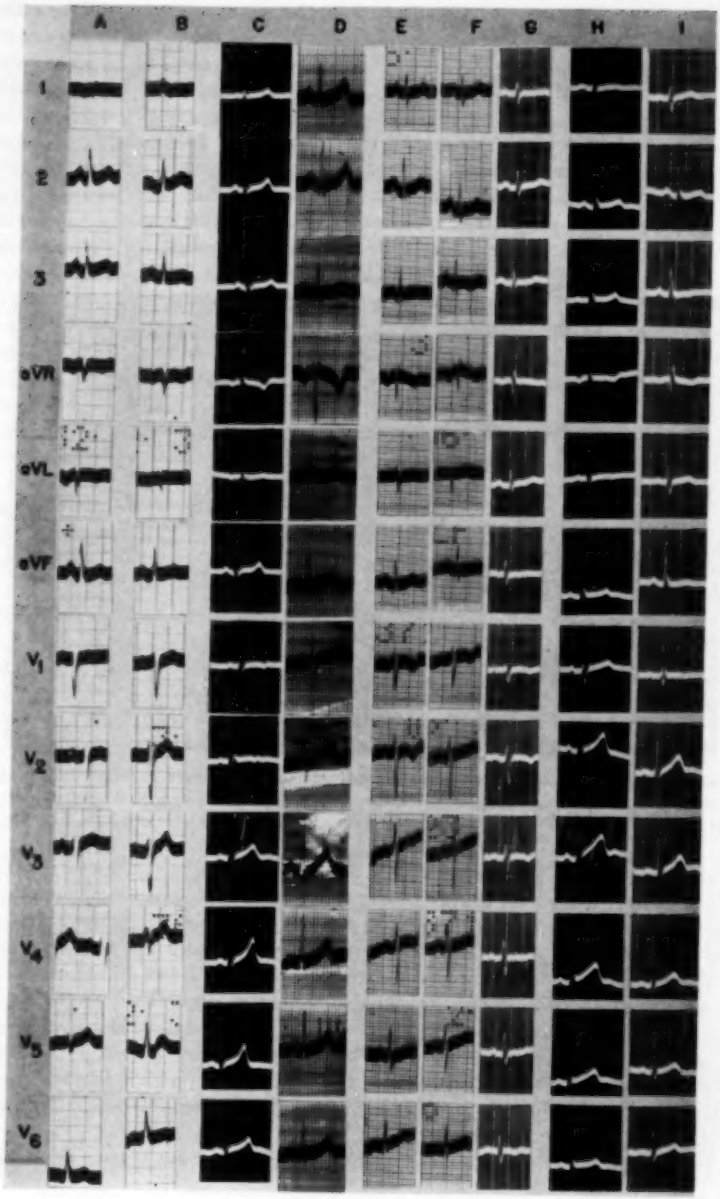

FIG. 2

surgery has been performed on one side, followed by the development of marked contralateral destructive or infiltrative disease, a critical reduction in the vascular bed of the lungs may occur with the production of acute cor pulmonale in the absence of pulmonary embolism (19). Since right ventricular dilatation and marked resultant clockwise rotation of the heart occur in acute cor pulmonale, the mechanism of such changes should be distinguished from the phenomena which are the subject of this paper.

After either right or left thoracoplasty, there was a tendency for the "electrical" position of the heart to become more horizontal, a change which was less marked, however, than that occurring after pneumonectomy (figures 2E, F, and G). Possibly, this was related to the frequently present scoliosis and rotation of the thoracic spine.

After pneumoperitoneum, because of the elevation of both leaves of the diaphragm, the heart became more horizontal and demonstrated some degree of counterclockwise rotation along its longitudinal axis (figures 2H and I). This change in both "electrical" and anatomical position of the heart would also be expected to occur after left phrenico-exeresis or intra-abdominal conditions accompanied by elevation of the diaphragm, such as obesity, pregnancy, or ascites.

SUMMARY

A study of the electrocardiographic changes occurring before and after pulmonary collapse therapy and before and after various types of thoracic surgery demonstrates that most of these changes are those which have been interpreted as reflecting changes in "electrical" position. It was seen that many of the changes in "electrical" position were readily correlated with similar changes in anatomic position as evidenced by roentgenographic control.

FIG. 2. Electrocardiograms of: A. A patient with a spontaneous right pneumothorax; and B, the same patient after re-expansion of the right lung. Notice that in B the electrical position has become less vertical, and counterclockwise rotation of the heart about its longitudinal axis has occurred, as evidenced by appearance of small R-wave and less inversion of P wave in aV_L and shift of transition zone in the chest leads to the right. C and D, before and after a right pneumonectomy in another patient. In D, the "electrical" position of the heart has become more horizontal with some counterclockwise rotation about its longitudinal axis since a tall R-wave is now present in lead I; P and QRS are small and upright in aV_L and the transition zone has moved to the right. E, before; F, one week after; and G, 4 months after a right thoracoplasty in a third patient. In G, the "electrical" position of the heart has become slightly more horizontal as evidenced by upright P and QRS in aV_L and deepening of S-wave in aV_F. There has been slight rotation of the heart in a counterclockwise fashion about its longitudinal axis as seen by a slight shifting of the transition zone in the precordial leads to the right. H and I, before and after a pneumoperitoneum in a fourth patient. The electrical position of the heart has become more horizontal in I and there has been some counterclockwise rotation about its longitudinal axis, as seen from the fact that R is taller in lead I, and smaller in lead III, an R wave is now present in aV_L, and the transition zone has moved to the right. This change may have been more marked had a phrenic crush with further elevation of the hemidiaphragm been added to this procedure.

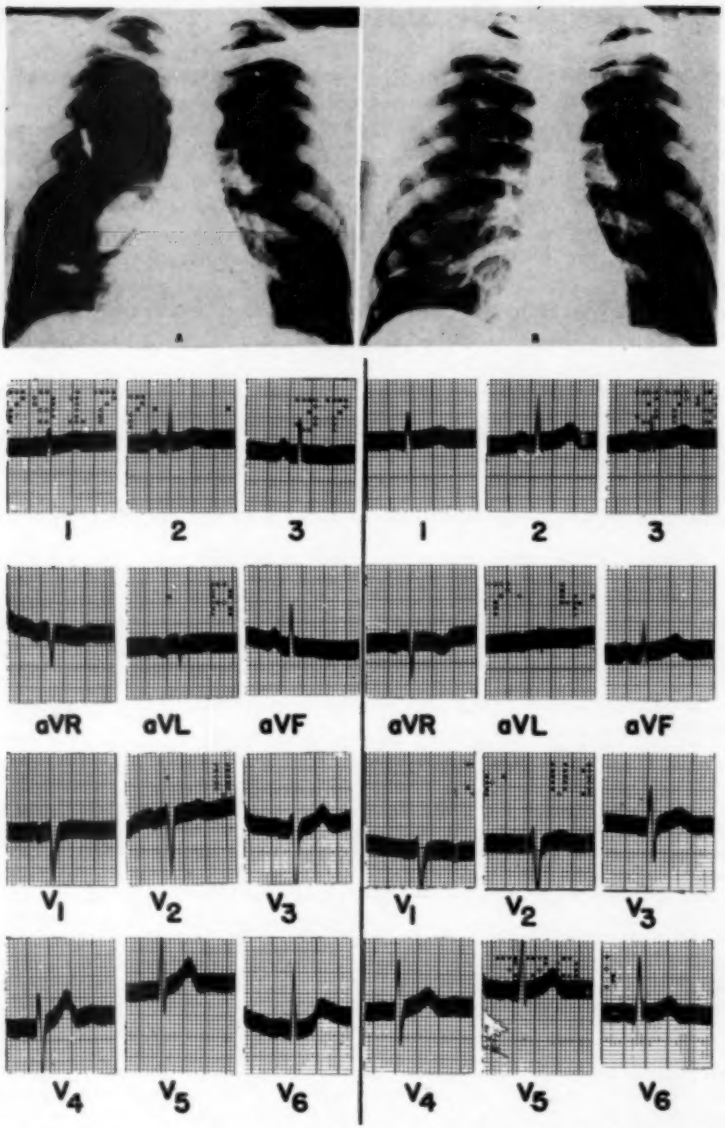

FIG. 3. Roentgenograms and electrocardiograms of a patient with a spontaneous right pneumothorax (A); and after the right lung had almost completely re-expanded (B). Notice that in B, after re-expansion, R is taller in I and smaller in III, P is less inverted and S is smaller in aV_L, R is smaller in aV_F, and the transition zone has shifted to the right. In the roentgenogram (A), the apparent widened transverse diameter of the heart is due to the fact that part of the density at the right border is composed of collapsed lung.

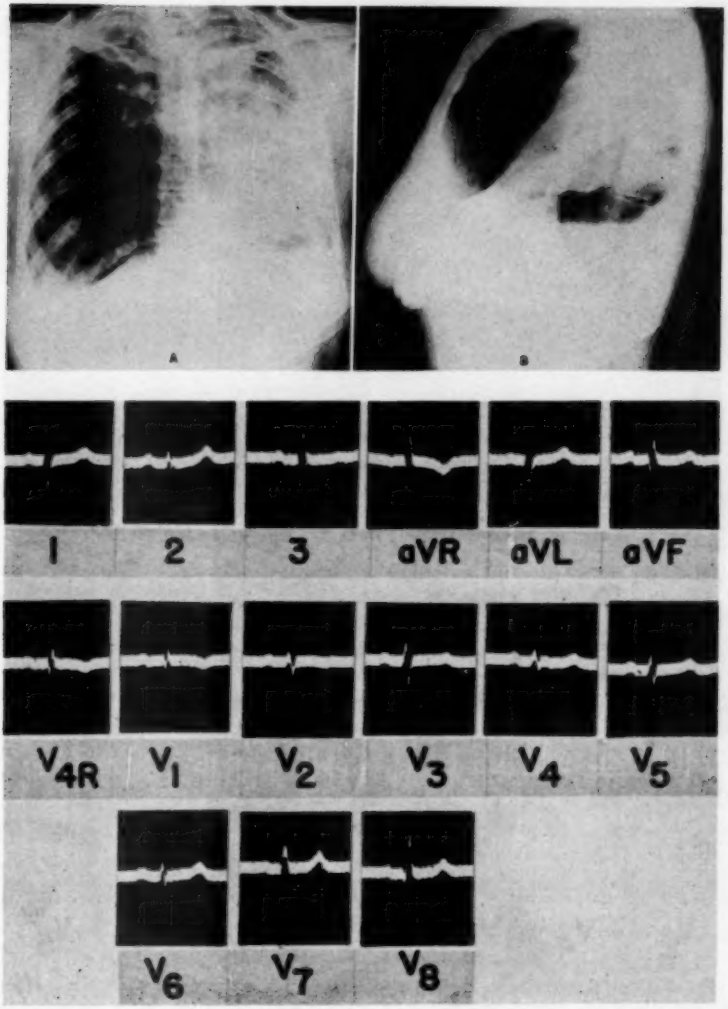

FIG. 4. Electrocardiograms and posterior-anterior (A) and lateral (B) roentgenograms from a patient with a markedly fibrotic and contracted left lung. In B, notice the marked increase in space between the anterior surface of the heart and the anterior chest wall. This is responsible for the reduced amplitude of the QRS complexes in the precordial leads (V_{4R} through V_6) and the relative increase in amplitude of the QRS complexes in the left midscapular line (V_8).

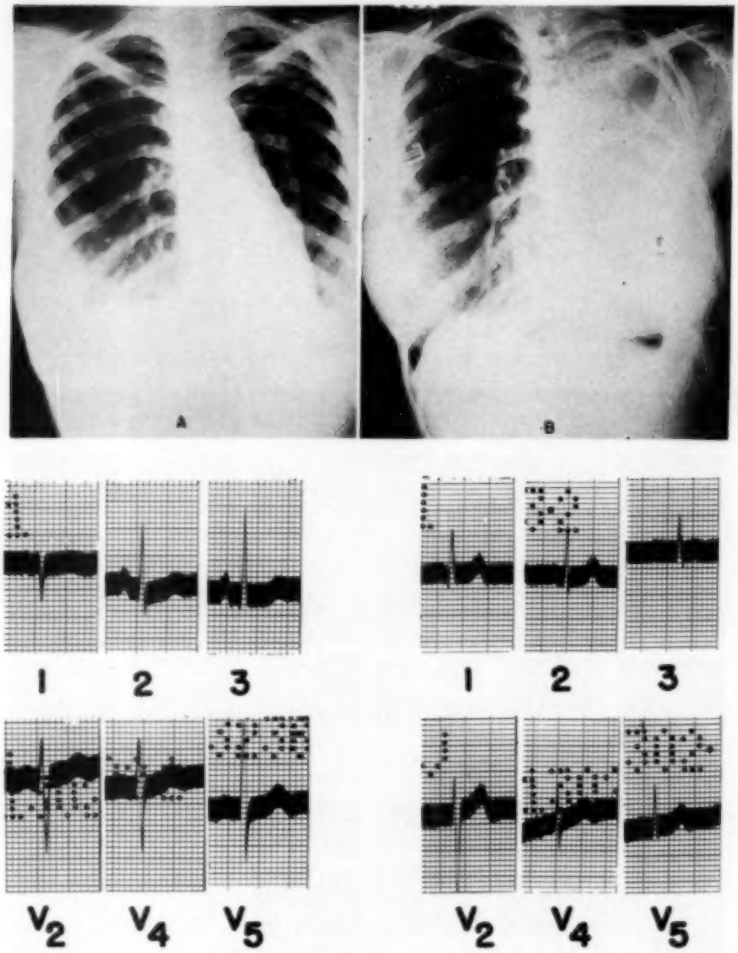

FIG. 5. Roentgenograms and electrocardiograms of a patient with a left pneumothorax (A) and after a left pneumonectomy (B) was performed. There has been a marked change in the appearance of the electrocardiogram, which is explained by the more horizontal position of the heart after pneumonectomy. A deep S in lead I has been replaced by an R, R in lead III is now smaller.

In both *right and left pneumothorax* the "electrical" position of the heart tended to become more vertical. The transition zone in the chest leads showed a tendency to be shifted to the left in patients with right pneumothorax. In left pneumothorax the amplitude of QRS in the chest leads became diminished because of the increased amount of air between the heart and anterior chest wall.

After either *right or left pneumonectomy* the "electrical" position of the heart became more horizontal. The shift in transition zone in the chest leads was seen to depend on the interval of time that had elapsed following the surgical procedure.

After either *right or left thorocoplasty* there was a slight tendency for the "electrical" position of the heart to become more horizontal.

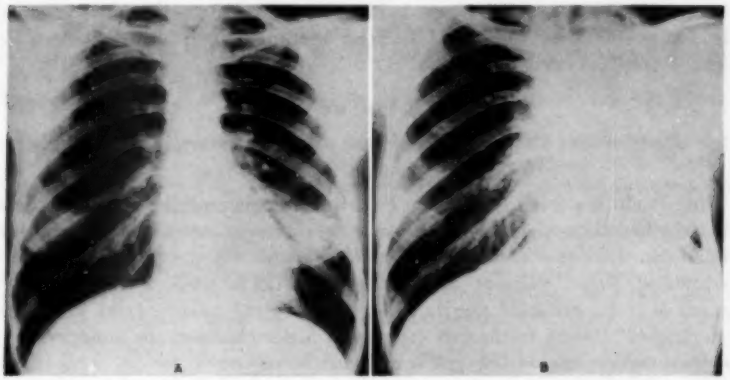

FIG. 6. Roentgenograms of a patient before (A) and twelve months after (B) a left pneumonectomy showing shift of the mediastinum to the left and elevation of the left diaphragm in B.

In patients with *pneumoperitoneum* the "electrical" position of the heart became more horizontal. The transition zone in the chest leads became displaced to the right.

SUMARIO

Alteraciones Electrocardiográficas que Acompañan a la Colapsoterapia Pulmonar y a la Cirugía Torácica

Un estudio de las alteraciones electrocardiográficas que sobrevienen antes y después de la colapsoterapia pulmonar y antes y después de la cirugía torácica demuestra que la mayor parte de las mismas son las interpretadas como reflejos de las alteraciones en la posición eléctrica. Observóse que muchas de las alteraciones en la posición eléctrica correlacionaban fácilmente con alteraciones semejantes en la posición anatómica según evidenciaba la comprobación roentgenográfica.

En el neumotórax tanto derecho cuanto izquierdo, la posición "eléctrica" del corazón solía volverse más vertical. La zona de transición en las derivaciones torácicas reveló tendencia a desviación a la izquierda en los enfermos con neumotórax derecho. En el neumotórax izquierdo, disminuyó la amplitud de la QRS en las derivaciones torácicas debido a la mayor cantidad de aire entre el corazón y la pared anterior del tórax.

Después de la neumonectomía ya derecha o izquierda, la posición "eléctrica" del corazón se volvió más horizontal. La desviación de la zona de transición en las derivaciones torácicas dependía, según se observó, del tiempo transcurrido desde el procedimiento quirúrgico.

Después de la toracoplastia ya derecha o izuierda, hubo leve tendencia de la posición "eléctrica" del corazón a volverse más horizontal.

En los enfermos tratados con neumoperitoneo, la posición "eléctrica" del corazón se volvió más horizontal. La zona de transición en las derivaciones torácicas se desplazó hacia la derecha.

RÉSUMÉ

Modifications électrocardiographiques associées à la collapsothérapie du poumon et à la chirurgie thoracique

Une étude des modifications de l'électrocardiogramme, se produisant avant et après la collapsothérapie et à la suite de diverses formes de chirurgie thoracique, démontre que la plupart de ces modifications sont celles qui ont été interprétées comme reflétant des modifications de la position "électrique" du coeur. Il a été constaté que beaucoup d'entre ces modifications de position "électrique" étaient facilement rapportées à des changements similaires de la position anatomique vérifiée par l'examen radiologique.

Dans le pneumothorax droit ou gauche, la position "électrique" du coeur tend à devenir plus verticale. La zone de transition des dérivations précordiales montre une tendance à la déviation vers la gauche chez les malades ayant un pneumothorax droit. Dans le pneumothorax gauche, l'amplitude de QRS des dérivations précordiales est diminuée en raison de l'augmentation de la quantité d'air entre le coeur et la paroi thoracique antérieure.

A la suite d'une pneumectomie droite ou gauche la position "électrique" du coeur est devenue plus horizontale. Il a été observé que la déviation de la zone de transition des dérivations précordiales dépendait de l'intervalle de temps écoulé depuis l'intervention chirurgicale.

A la suite de la thoracoplastie droite ou gauche la position "électrique" du coeur montrait une légère tendance à devenir plus horizontale.

Chez les malades ayant un pneumopéritoine la position "électrique" du coeur est devenue plus horizontale. La zone de transition des dérivations précordiales s'est déplacée vers la droite.

Acknowledgment

The authors wish to express their grateful appreciation to Dr. Louis N. Katz and Dr. David B. Radner for their criticism and suggestions in this study.

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THE ELECTROCARDIOGRAM IN PATIENTS WITH MEDIASTINAL SHIFT TO THE LEFT[1]

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(Received for publication March 23, 1951)

INTRODUCTION

The purpose of this report is to describe the electrocardiographic changes which may occur in pulmonary tuberculosis when there is shift of the heart and mediastinum to the left as a result of the disease or its therapy. The literature on the subject is sparse and usually limited to consideration of the standard leads and a single precordial lead. The present study includes the so-called unipolar limb leads and multiple precordial unipolar leads. Knowledge of these electrocardiographic changes is sometimes important in the differential diagnosis of electrocardiographic abnormalities in patients with pulmonary tuberculosis.

OBSERVATIONS

Case Material

Electrocardiograms were done on 10 patients who showed some degree of shift of the heart and mediastinum to the left in the postero-anterior chest roentgenogram. Tracings were made with the patient in the recumbent position. Twelve leads were taken in each case, including the 3 standard limb leads, the 3 augmented unipolar (aV) limb leads, and 6 unipolar precordial (V) leads from chest positions 1 to 6, as defined by the American Heart Association. The various leads used in this study may be described as follows:

Leads I, II, and III are the bipolar standard limb leads.

Leads aV_R, aV_L, and aV_F are Goldberger's augmented unipolar limb leads for the right arm, left arm, and left leg, respectively (see Goldberger, *Unipolar Lead Electrocardiography*, Lea and Febiger, Philadelphia, 1947).

Leads V_1 to V_6 are the six unipolar precordial leads using the Wilson terminal for the indifferent electrode with the exploring electrode on chest positions 1 to 6 (see American Heart Association: Standardization of precordial leads, Am. Heart J., 1938, *15*, 107 and 235).

There were 5 male and 5 female patients, and their ages ranged from 26 to 60 years (table 1). The degree of mediastinal shift was partial in 4 and complete in 6 cases. Shift was due to reduced left lung volume in 7 cases and to pneumonectomy in 3 cases. The electrocardiograms were done months after pneumonectomy so that fluid absorption and fibrosis with consequent mediastinal shift were maximal. Pneumoperitoneum was also present in 4 patients, including

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TABLE 1

Clinical and Electrocardiographic Characteristics in Patients with Mediastinal Shift to the Left

CASE NUMBER	SEX	AGE	DEGREE OF SHIFT	CAUSE OF SHIFT	COMPLICATIONS	ELECTROCARDIOGRAPHIC CHARACTERISTICS			
						Limb Leads		Precordial Leads	
						Axis Deviation	Electrical Position	Transitional Zone	T-Wave Pattern
1	M	60	partial	partial atelectasis		R	horizontal	V_5–V_4	normal
2	M	42	partial	partial atelectasis		R	vertical	V_5–V_4	normal
3	M	60	partial	partial atelectasis	contralateral disease	L	semi-horizontal	V_2–V_4	normal
4	F	28	partial	pneumonectomy	pneumoperitoneum	R	vertical	V_1–V_2	low V_4–V_6
5	F	40	complete	complete atelectasis		R	vertical	V_4–V_5	inverted V_1–V_4
6	F	26	complete	pneumonectomy	bronchiectasis	R	vertical	V_5–V_6	all low
7	F	31	complete	complete atelectasis	contralateral disease	R	vertical	V_5–V_4	flat V_1–V_4
8	F	35	complete	pneumonectomy	pneumoperitoneum	R	vertical	V_6–V_5	inverted V_1–V_6
9	M	26	complete	complete atelectasis	pneumoperitoneum; contralateral disease	L	indeterminate	V_5–V_6	inverted V_1–V_4
10	M	29	complete	complete atelectasis	pneumoperitoneum; Lucite sphere plombage; contralateral disease	R	vertical	none (all Rs)	inverted V_1–V_6

2 with pneumonectomy and 2 with atelectasis. In one of these 4 patients the mediastinal shift was partial and in the other 3 it was complete. In one patient with complete shift due to atelectasis with pneumoperitoneum, there was also a Lucite sphere plombage on the left (Case 10). None of the 10 patients showed any clinical evidence of chronic cor pulmonale. In 3 patients with complete atelectasis of the left lung there was some contralateral disease.

Electrocardiographic Changes

Electrical position of heart: Right axis deviation was present in 8 of the 10 cases (table 1). The electrical position of the heart as determined from the unipolar limb leads was vertical in 7 of the patients. No consistent T-wave changes in the limb leads were noted that could be correlated with the anatomic position of the heart in the chest.

Precordial leads: On analysis of the precordial leads, the location of the transitional zone of the QRS complexes was normal (1) in 9 cases, although somewhat shifted to the right in one case and somewhat shifted to the left in 3 cases. It was indeterminate in Case 10 in which all complexes in the precordial leads were of the Rs type (figure 1). No correlation could be made between the location of the transitional zone and the anatomical position of the heart in the chest. This is probably due to the fact that the direction and degree of rotation of the heart around its long axis cannot be determined from the roentgenogram, and the position of the transitional zone is in part dependent upon such rotation since it reflects the relationship of the interventricular septum to the anterior chest wall. In the single case which showed a shift of the transitional zone to the right (Case 4), there was a very high left diaphragm due to paralysis and pneumoperitoneum. This probably caused counterclockwise rotation of the heart around its long axis, as viewed from the apex.

Precordial T-wave pattern. The precordial T-wave pattern was more consistent. It was normal in 3 patients having only partial mediastinal shift (for example: Case 1, figure 1). In the fourth case of partial shift the T-waves in V_4 to V_6 were low, along with small amplitude of the QRS complexes in V_5 and V_6. This can be explained by the presence of a very high left diaphragm and pneumoperitoneum so that air was interposed between the heart and the chest wall in these precordial positions (2). By contrast, in those patients who showed a marked shift of the heart into the left chest, there was definite flattening or inversion of the T-waves from V_1 to V_4, V_5, or even V_6 (illustrated by Cases 6 to 10 in figure 1). These changes were definitely abnormal by comparison with a large series of normals (1), for T-waves occasionally may be inverted as far to the left as V_2, but never in V_4. Further, the minimum height of an upright T in normals with right axis deviation is given as 2.0 mm. in V_3, 1.0 mm. in V_4, and 2.0 mm. in V_5. There were 2 patients in the present series (Cases 6 and 7) with marked mediastinal shift that had upright precordial T-waves in V_2, V_4, or V_5. These patients had right axis deviation, and the T-waves in the aforementioned precordial leads were lower than the minimum normal height given above.

Precordial T-wave inversion was most marked in 2 cases in which pneu-

moperitoneum was present in addition to marked cardiac shift due to atelectasis of the lung (Cases 9 and 10). In one of these cases the QRS pattern in the precordial leads suggested right ventricular hypertrophy (Case 10).

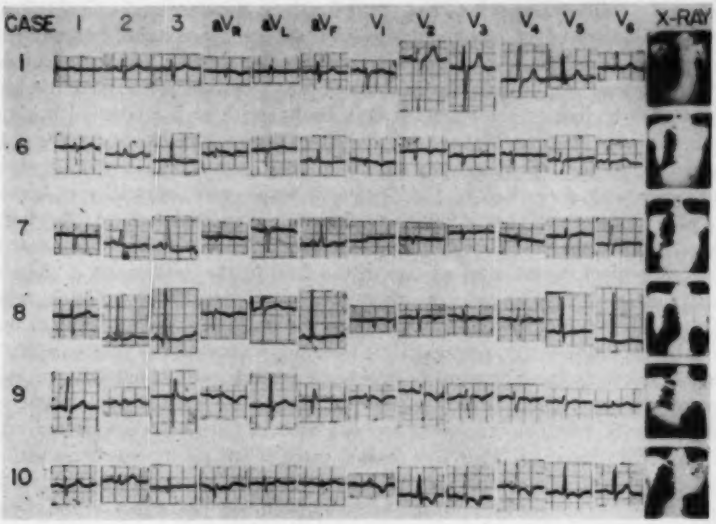

FIG. 1. Electrocardiograms and postero-anterior chest roentgenograms for representative cases. Indicated across the top of the figure are the various leads, including: standard limb leads I, II, and III; augmented unipolar limb leads aV_R, aV_L, and aV_F; and unipolar precordial leads V_1 to V_6. The following cases are included:

Case 1: Partial mediastinal shift with a normal electrocardiogram except for low T_1.
Case 6: Complete mediastinal shift due to pneumonectomy.
Case 7: Complete mediastinal shift due to atelectasis complicated by contralateral disease.
Case 8: Complete mediastinal shift due to pneumonectomy complicated by pneumoperitoneum.
Case 9: Complete mediastinal shift due to atelectasis complicated by pneumoperitoneum and contralateral disease.
Case 10: Complete mediastinal shift due to atelectasis complicated by pneumoperitoneum, left Lucite sphere plombage and contralateral disease. Note pattern of right ventricular hypertrophy in precordial leads.

In summary, most patients showed right axis deviation and an electrically vertical position of the heart, but the degree of mediastinal shift correlated best with changes in the precordial T-wave pattern.

DISCUSSION

There are several factors other than mediastinal shift which may influence the electrocardiographic pattern in these cases. These factors are: (a) pneumoperitoneum, (b) pneumonectomy, and (c) subclinical chronic cor pulmonale.

The effects of pneumoperitoneum are minimal. In an excellent investigation and review of the subject, Pollak (3) concludes that pneumoperitoneum has no significant effect on the electrocardiogram taken in the recumbent position, including all the leads used in the present study. The majority of patients show a normal electrocardiogram with a vertical axis in standard and unipolar leads.

The long-term effect of pneumonectomy, on the other hand, has not been thoroughly studied. A few cases were reported prior to 1949, but these had electrocardiograms only during the immediate postoperative period and the leads taken were limited to the standard limb leads and 1 or 2 precordial leads (4, 5, 6). In 1949 Biocca, Masini, and Sposito (7) reported electrocardiographic studies in 50 cases of lobectomy or pneumonectomy. These authors mention late permanent alterations of the T-wave in some cases, especially in leads I, II, V_4, and V_6, which they interpret as signs of myocardial damage following an initial pericarditis. It should be noted that mediastinal shift does not occur for some time after pneumonectomy, until the fluid in the dead space is absorbed and replaced by scar tissue. Furthermore, most pneumonectomies in tuberculous patients are followed by thoracoplasty in order to avoid mediastinal shift. At this hospital recently, postoperative pneumoperitoneum has been substituted for thoracoplasty in an attempt to avoid or minimize mediastinal shift following pneumonectomy. This was only partially successful in Case 4 and was unsuccessful in Case 8. Pneumoperitoneum was not used in Case 6 because it proved to be a painful procedure. Therefore these 3 cases of left pneumonectomy without thoracoplasty were available for this study. From the material described in this paper, it would appear that pneumonectomy itself has little effect on the electrocardiogram because the changes in the precordial T-wave pattern were similar in cases with or without pneumonectomy. However, it must be admitted that the number of cases is small.

Subclinical chronic cor pulmonale also merits consideration as a factor which might influence the electrocardiographic pattern in addition to the factor of mediastinal shift. Certainly, in long-standing pulmonary tuberculosis of extensive nature, right ventricular hypertrophy occurs to some degree and right ventricular failure is often a terminal manifestation. However, right ventricular hypertrophy begins to occur before clinical or electrocardiographic evidence of the fact appears. Therefore, without actual measurement of the pulmonary arterial pressure or the thickness of the right ventricular wall, it is impossible to say how much effect such a factor might have in the production of the electrocardiographic changes described in these cases. Electrocardiographic pattern has been correlated with pulmonary arterial pressure in patients with chronic pulmonary disease by Cournand and his associates (8), and it appears that diagnostic patterns do not occur unless the pulmonary arterial pressure is markedly increased. However, these authors confined their electrocardiographic observations to the QRS complex. There is a definite precordial lead pattern (8, 9, 10) which is characteristic of right ventricular hypertrophy as exemplified by Case 10 (figure 1) in this series. With this pattern the precordial leads show Rs complexes with late intrinsicoid deflections and inverted T-waves over the right precordium. Nevertheless, such a pattern is a relatively late manifestation

of chronic cor pulmonale. Moreover, the possibility cannot be excluded that the precordial T-wave changes in the other cases of marked mediastinal shift may be due, in part, to lesser degrees of right ventricular hypertrophy instead of mediastinal shift alone. Precordial T-waves tend to be lower in cases of right ventricular hypertrophy than in normal persons (10).

Eventually, many cases of tuberculosis with mediastinal shift go on to develop symptoms of cardiac embarrassment (11) due to reduction in the pulmonary capillary bed and compensatory emphysema in the nonatelectatic lung, distortion of the great vessels, fixation of the chest wall, and subclinical anoxia caused by respiratory insufficiency. The fact that the deepest precordial T-wave inversions occurred in Cases 9 and 10 may be significant. These patients had complete atelectasis of the left lung with contralateral disease and pneumoperitoneum. This combination of factors, not present in any other case in this series, would produce the most marked dislocation of the heart but might also be most likely to produce right ventricular hypertrophy. Therefore, although it appears that the precordial T-wave pattern is best correlated with the degree of change in heart position, the possibility of subclinical chronic cor pulmonale as a factor in these T-wave changes must be given serious consideration.

There is need for continued study of the electrocardiographic changes due to pulmonary tuberculosis and its therapy in order to evaluate the electrocardiogram in such patients.

SUMMARY

Shift of the heart and the mediastinum to the left in pulmonary tuberculosis is associated with changes in the electrocardiogram. Most cases show right axis deviation and vertical electrical position of the heart. When the shift of the heart is marked, most of the T-waves in multiple precordial leads are flattened or inverted. The electrocardiographic pattern may be complicated by the effect of subclinical chronic cor pulmonale.

SUMARIO

El Electrocardiograma en los Enfermos con Desviación del Mediastino a la Izquierda

La desviación del corazón y del mediastino hacia la izquierda en la tuberculosis pulmonar va unida a alteraciones electrocardiográficas. La mayor parte de los casos muestran desviación del eje a la derecha y posición eléctrica vertical del corazón. Cuando la desviación del corazón es pronunciada, la mayor parte de las ondas en T de las derivaciones precordiales múltiples están aplanadas o invertidas. El patrón electrocardiográfico puede ser complicado por el efecto de un cor pulmonale crónico subclínico.

RESUME

L'électrocardiogramme chez les malades présentant une déviation du médiastin vers la gauche

Dans la tuberculose pulmonaire la déviation du coeur et du médiastin vers la gauche s'accompagne de modifications de l'électrocardiogramme. Dans la plupart

des cas l'axe est dévié vers la droite indiquant que le coeur est en position "électrique" verticale. Quand la déviation de la position du coeur est marquée, la plupart des ondes T dans les diverses dérivations précordiales sont aplaties ou inversées. Le tracé de l'électrocardiogramme peut être modifié par les manifestations subcliniques de l'hypertrophie du ventricule droit.

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EVALUATION OF THE HEMAGGLUTINATION REACTION IN THE DIAGNOSIS OF ACTIVE TUBERCULOSIS[1]

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(Received for publication February 16, 1951)

INTRODUCTION

Great interest has been aroused in the diagnostic potentialities of a hemagglutination test for tuberculosis described by Middlebrook and Dubos in 1948 (1). No claims were made by Middlebrook and Dubos concerning the diagnostic value of the test, but their observations gave rise to the hope that this reaction might have greater specificity than other serologic procedures, such as the complement fixation test, and that a positive test would be indicative of active tuberculous infection.

The results of attempts to utilize the hemagglutination reaction in the diagnosis of active tuberculosis have been somewhat contradictory. Rothbard (2) obtained positive reactions in a titer of 1:8 or higher in 92 per cent of 168 patients with active tuberculosis and negative reactions in 31 of 33 patients with arrested pulmonary tuberculosis. Of 216 persons who were healthy, or who had various nontuberculous diseases, negative reactions were obtained in 203; and in the other 13, the reaction titers were 1:2 or 1:4. It was concluded that the reaction was quite specific for tuberculosis and that a titer of 1:8 or higher was highly suggestive of the presence of an active tuberculous process.

Smith (3), on the other hand, observed hemagglutinins in the sera of a number of persons who reacted to tuberculin but who had no evidence of active tuberculosis. In others, hemagglutinins developed following the performance of a tuberculin test. Positive reactions were obtained in 80 per cent of 104 patients with active tuberculosis, but no distinction was made between titers higher or lower than 1:8. Of the 24 patients with active tuberculosis for whom specific data were presented, titers below 1:8 were recorded in 7 (29 per cent). Smith concluded that the hemagglutination reaction "is not a test for determining the clinical activity of a tuberculous lesion."

A number of studies have also appeared recently in the French literature (4, 5, 6). The French workers, in general, have confirmed the observations of Rothbard and regard the test as being of considerable aid in diagnosis.

The purpose of this report is to present the results of hemagglutination studies which were performed on sera from 315 adult patients, most of whom were admitted to the infectious disease ward of the King County Hospital. Blood was drawn on admission, and the tests were performed promptly so that the results could be evaluated from the standpoint of aid in diagnosis. Fifty-four of the 315 patients were subsequently proved to have active tuberculosis, and 10 patients had tuberculous lesions which were considered arrested at the time the test was performed.

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METHODS AND MATERIALS

The modification of the hemagglutination test described by Smith (3) was used for this study. This technique differs in only a few minor respects from that of Middlebrook and Dubos (1), and of Rothbard (2). A number of sera were tested by all three methods, and significant differences in titers were not observed. The antigen, Lederle's Old Tuberculin concentrated four times,[1] was the same as that employed by both Rothbard and Smith.

A hyper-immune rabbit serum was used as a positive control whenever the tests were performed, and it consistently gave a titer of 1:1024 with the antigen used.

The majority of the tests were performed prior to tuberculin testing since the blood specimens were obtained from acutely ill patients on admission to the hospital. It is possible that in a few instances a tuberculin test might have been performed shortly before admission to the hospital, but this was fairly well excluded by questioning the patients.

RESULTS

Serum from nontuberculous persons: The hemagglutination reaction was determined in the sera of 251 patients with nontuberculous diseases (table 1). Most of these patients were suffering from acute infections, with respiratory infections and poliomyelitis predominating. The possibility that an active tuberculous process might be present was considered in every case and was excluded only after careful observation. A special effort was made to look for signs and symptoms of tuberculosis, and chest roentgenograms were obtained in more than 90 per cent of the cases. The patients who were not examined roentgenographically all had poliomyelitis, and none have developed signs or symptoms of tuberculosis during a follow-up period of observation of at least four months. Examinations of the sputum for *M. tuberculosis* were made in all patients with respiratory infections, and they were followed in the chest clinic until all signs of pulmonary infiltration had disappeared from roentgenograms of the chest.

Negative hemagglutination reactions were observed in the sera of 128 (50 per cent) of the 251 nontuberculous patients. In the other 123 patients, hemagglutination occurred in titers ranging from 1:2 to 1:64. In most instances, the titers were 1:2 or 1:4 although in 24 patients (10 per cent) the serum yielded a positive reaction in a titer of 1:8 or higher. Of the 66 patients with acute poliomyelitis, titers of 1:8 or higher were observed in 11 (16 per cent).

Serum from patients with tuberculosis: Of the 64 patients with tuberculosis, the lesions of 54 were considered active, and in the other 10 persons the lesions were considered to be arrested (table 2). Patients with pulmonary tuberculosis were considered to have active disease on the basis of progressive changes in the roentgenograms, persistent fever, and the repeated demonstration of *M. tuberculosis* by culture of sputum or gastric aspirates. In all 5 patients with tuberculous meningitis, tubercle bacilli were recovered by culture of the cerebrospinal fluid. The initial findings and clinical course in the patients with pleurisy with effusion were in all instances compatible with a diagnosis of tuberculosis, but tubercle bacilli were cultured from the pleural fluid in only 3 of the 6 cases. In the one patient with tuberculous pericarditis, tubercle bacilli were cultured from both the sputum and the pericardial fluid.

[1] Dr. H. D. Piersma, of the Lederle Laboratories, generously supplied the Old Tuberculin used in this study.

TABLE 1

Results of Hemagglutination Tests Performed on the Sera of 251 Patients with Nontuberculous Diseases

DIAGNOSIS	NUMBER	NEGATIVE	1:2	1:4	1:8	1:16	1:32	1:64
Nontuberculous bacterial pneumonia	87	49	16	14	3	3	2	
Poliomyelitis	66	27	14	14	8	2		1
Lung abscess	7	3	2	1	1			
Tracheobronchitis, acute	18	11	4	3				
Bronchiectasis	9	4	3	2				
Chronic bronchitis	13	7	2	2	2			
Empyema, acute	6	3	3					
Fevers of unknown origin	8	4	3	1				
Streptococcal pharyngitis	6	4	2					
Congestive heart failure	8	3	3	1		1		
Pulmonary infarction	5	3	2					
Meningitis	6	4	1	1				
Infectious mononucleosis	4	3	1					
Measles	4	1	2	1				
Chickenpox	3	2	1					
Typhoid carrier	1				1			
Totals	251	128	59	40	15	6	2	1

TABLE 2

Results of Hemagglutination Tests in 64 Patients with Active or Apparently Arrested Tuberculosis

DIAGNOSIS	NUMBER	NEGATIVE	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256
Pulmonary Tuberculosis										
Minimal	3	1	2							
Moderately advanced	10	2	0	1	2	3	2			
Far advanced										
Seriously but not terminally ill	26	0	2	2	7	5	6	2	1	1
Terminally ill	3	3								
Apparently arrested	10	3	2	3	2					
Extrapulmonary Tuberculosis										
Meningitis										
Terminally ill	2	2								
Moderately ill	3	1	2							
Pleurisy with effusion										
(Tuberculous etiology proved)	3	1	1		1					
(Tuberculous etiology not proved)	3	2			1					
Pericarditis	1			1						
Totals	64	15	9	7	13	8	8	2	1	1

In 31 of the 54 patients with active tuberculosis the hemagglutination reaction was positive in titers of 1:8 or higher. If the patients with pulmonary tuberculosis alone are considered, 29 (75 per cent) of the 39 with moderately or far advanced disease yielded positive hemagglutination reactions in titers of 1:8 or higher. On the other hand, a completely negative reaction was observed with the sera of 12 patients with active tuberculosis. As may be seen in table 2, 5 of these patients were terminally ill and died within four days after admission to the hospital.

DISCUSSION

In the present study, hemagglutinins were detected in the sera of approximately 50 per cent of 251 patients with nontuberculous diseases, and in 24 patients (10 per cent) the reactions were positive in a titer of 1:8 or higher. This relatively high incidence of positive reactions in sera from nontuberculous persons sharply limited the diagnostic value of the test in any given case.

The diagnostic value of the test was further limited by the fact that titers of 1:8 or higher were obtained in the serum of only 57 per cent of the patients proved to have active tuberculosis. In 10 patients with active tuberculosis, the reactions were completely negative. Five of these patients were terminally ill when the blood was drawn, but the others were not. In situations in which the test would have been of the greatest diagnostic value, i.e., tuberculous meningitis, pericarditis, and pleurisy with effusion, the reactions were negative, or positive only in low titers in most instances. Of the 39 patients with moderately or far advanced pulmonary tuberculosis, a positive hemagglutination reaction in a titer of 1:8 or higher was recorded in 29, or 75 per cent. However, in these patients the diagnosis was easily established within the first day or two by finding tubercle bacilli in the sputum.

The results obtained in the present study are in fair agreement with the observations of Smith, but are at variance with those of Rothbard. The data obtained by these authors have been summarized in the introduction. The technique described by Smith was used in the present study and differs in only minor respects from the procedure employed by Rothbard. The present writers have repeatedly tested sera by both methods, and have been unable to observe significant differences in the titer of the reaction. It is difficult to account for the discrepancies between the present results and those obtained by Rothbard. Particularly striking is the fact that in his series "false positive" reactions were not observed; and in the great majority of persons without evidence of active tuberculosis, hemagglutinins were absent from the serum altogether.

It should be stressed that Middlebrook and Dubos have made no claims concerning the diagnostic value of the hemagglutination reaction. Their emphasis has been on the usefulness of the reaction in studying various immunologic processes in relation to tuberculosis.

The hemagglutination test as performed in the studies so far reported has utilized concentrated Old Tuberculin to sensitize the erythrocytes. Old Tuberculin is a crude product containing many substances which might become ad-

sorbed onto the surface of erythrocytes and give rise to "false positive" reactions. Attempts are being made to isolate fractions from this crude material which are relatively pure from a chemical standpoint and which may give greater specificity to the reaction. In addition, recent evidence (7) indicates that the incorporation of complement into the system, with the recording of hemolysis rather than agglutination of erythrocytes, may give results which are more indicative of the presence of active tuberculous infection. It appears that exploration of the potentialities of the hemagglutination reaction may well lead to a test which would be of value in studying patients suspected of having active tuberculosis.

SUMMARY

Among 251 patients with nontuberculous diseases, mostly acute infections, hemagglutinins were present in the sera of 123, and in 24 (10 per cent), the hemagglutination reaction was present in a titer of 1:8 or higher.

In 31 (57 per cent) of 54 patients with active tuberculosis, the reaction was positive in a titer of 1:8 or higher. Of 39 patients with moderately or far advanced pulmonary tuberculosis, 29 (75 per cent) were found to have hemagglutinins in a titer of at least 1:8. In contrast, the reaction was negative in the sera of 10 patients with active tuberculosis. In patients with tuberculous meningitis, pericarditis, and pleurisy with effusion, the reaction was negative, or positive only in low titers, in most instances.

The test was of little practical aid in diagnosis since *M. tuberculosis* could be readily demonstrated in the sputum of most of the patients with high hemagglutination titers, and positive reactions occurred in 10 per cent of persons with nontuberculous conditions.

SUMARIO

Valuación de una Prueba de Hemaglutinación en el Diagnóstico de la Tuberculosis Activa

Entre 251 enfermos con afecciones no tuberculosas, en su mayoría infecciones agudas, había aglutininas presentes en los sueros de 123, y en 24 (9.6 por ciento), los títulos eran de 1:8 ó más altos.

De 54 enfermos con tuberculosis activa, 31 (57 por ciento) tenían títulos de 1:8 o más. De 39 con tuberculosis pulmonar moderadamente o muy avanzada, 29 (75 por ciento) reaccionaron a una dilución a lo menos de 1:8. Por otro lado, obtuviéronse resultados negativos en los sueros de 10 enfermos con tuberculosis activa. En los pacientes con meningitis tuberculosa, pericarditis y pleuresía con derrame, la reacción fué negativa o a lo más positiva a bajo título, en la mayoría de los casos.

La prueba resultó de poco valor práctico en el diagnóstico, dado que se hicieron exámenes positivos del esputo sin dificultad en la mayor parte de los enfermos con elevados títulos de hemaglutinación, y hubo reacciones positivas en 10 por ciento de los individuos con estados no tuberculosos.

RESUME

Evaluation du test d'hémo-agglutination pour le diagnostic de la tuberculose évolutive

Parmi 251 malades atteints d'affections non tuberculeuses, pour la plupart des infections aiguës, les hemo-agglutinines ont été trouvée dans le sérum chez 123 d'entre eux et chez 24 (10%) le titre était de 1/8ème ou plus élevé. Sur 54 malades atteints de tuberculose en activité, 31 (57%) avaient des taux de 1/8 ou supérieurs. Chez 39 malades dont la tuberculose pulmonaire était moderée ou très avancée le sérum de 29 d'entre eux (75%) réagissait à une dilution d'au moins 1/8. D'autre part des tests négatifs ont été obtenus avec le sérum de 10 malades affectés de tuberculose en évolution. Chez des malades atteints de méningite tuberculeuse, de péricardite et de pleurésie avec épanchement, dans la plupart des cas le test s'est montré négatif ou parfois positif, mais uniquement dans le cas de titre faible.

En pratique le test ne s'est pas montré très utile étant donné que des examens de crachats positifs étaient obtenus facilement chez la plupart des malades ayant un titre d'hémo-agglutination élevé; de réactions positives se sont produites chez 10% des sujets atteints d'affections non tuberculeuses.

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POTASSIUM IODIDE AND PARA-AMINOSALICYLIC ACID (PAS) IN CHRONIC FIBROID PULMONARY TUBERCULOSIS[1,2]

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Reports are contradictory concerning the use of potassium iodide as an adjunct to streptomycin therapy (1, 4). The present study was undertaken to determine the possible usefulness of potassium iodide with para-aminosalicylic acid (PAS) in the treatment of patients with chronic fibroid tuberculosis.

Clinicians have long believed that potassium iodide is contra-indicated in tuberculosis because of the fear that it leads to spread of the disease. Although iodides quickly permeate the extracellular fluids throughout the body, they do not permeate the tissue cells in general, whether the cells be normal or pathological. Iodides are excreted in part by way of the bronchial mucosa and cause irritation of tissues, but beyond this their exact mechanism of action is not clearly understood.

Syphilitic gummas are reported to resolve under treatment with potassium iodide, and it is feared that the walled-off tuberculous lesion might do likewise. Jobling and Peterson (2) state that iodides inactivate antiferments in the blood and inhibit antiferment activity of the lipoids of the lesion, thus favoring proteolysis of caseous material.

Despite these fears, potassium iodide has often been given to tuberculous patients without any evidence that it exerted an injurious effect. Moreover, the instillation of lipiodol is believed to be innocuous although it raises the blood iodine to high levels for a period of many months.

In a previous report (3) the writer has pointed out that PAS is relatively ineffective in chronic fibroid pulmonary tuberculosis. The present report is concerned with roentgenographic and bacteriologic studies in two groups of tuberculous patients: one group treated with PAS alone; the other, with PAS plus potassium iodide.

METHOD

The patients used in this study were predominantly middle-aged male patients with chronic fibrocavitary disease with sputum positive for *M. tuberculosis*. All previous efforts to control the disease had failed and they were kept mainly for custodial care. All were ambulatory and afebrile. Alternate cases were placed in each group. (Unequal numbers remained in each group at the end of the courses of treatment because of discharges against medical advice.)

The sodium salt of para-aminosalicylic acid, 4 gm. four times daily, was given to both groups as a liquid preparation. The second group received also potassium iodide, 0.25 gm. four times daily. Treatment was given daily for four months, followed by a rest interval of one or two months, then repeated. A total of 116 patients were started on therapy. Five

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[1] From the Municipal Tuberculosis Sanitarium of Chicago.

[2] Presented before the Chicago Tuberculosis Society, February 16, 1951.

were unable to take the PAS because of gastrointestinal difficulties. A considerable number were lost from observation because of discharges against medical advice. Sixty-five patients remained to finish one complete course of treatment; and, of these, 47 remained to complete a second course.

Roentgenograms of the chest were evaluated at four to six months after the commencement of the first course of treatment and again at eight to eleven months from that time. The post-treatment roentgenograms were described in comparison to the pre-treatment films in the following terms: (*1*) worse, (*2*) the same, (*3*) slightly improved, (*4*) moderately improved, and (*5*) markedly improved. *Slight improvement* was defined as 10 to 25 per cent in the abnormal roentgenographic shadows; *moderate improvement*, as 25 to 50 per cent; and *marked improvement*, as more than 50 per cent clearing. To avoid bias in judging the roentgenograms, they were mixed indiscriminately and rated without knowledge of the patient's treatment.

Sputum results were based on microscopic examination of twenty-four-hour concentrated specimens.

RESULTS

The results of analysis of the roentgenograms are shown in table 1. The large majority of the patients showed little or no change in the roentgenographic appearance after therapy. There is no evidence that potassium iodide in the dosage

TABLE 1

The Evaluation of Roentgenographic Changes at Specified Intervals in Patients Treated with Para-Aminosalicylic Acid (PAS) or with Para-Aminosalicylic Acid (PAS) Plus Potassium Iodide (KI)

	FOUR TO SIX MONTHS AFTER BEGINNING OF TREATMENT 65 PATIENTS				EIGHT TO ELEVEN MONTHS AFTER BEGINNING OF TREATMENT 47 PATIENTS			
	PAS		KI plus PAS		PAS		KI plus PAS	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Worse	0	0	1	4	4	14	1	6
No change	30	79	17	63	16	55	12	16
Slight improvement	6	16	7	26	5	17	4	22
Moderate improvement	2	5	2	7	4	14	1	6
Marked improvement	0	0	0	0	0	0	0	0
Totals	38	100	27	100	29	100	18	100

employed had a harmful effect on the course of the tuberculosis. Of the patients who showed improvement, the distribution between the two groups is not statistically significant. Marked improvement was conspicuous by its absence. At the end of four months of treatment the PAS-treated group showed improvement in 21 per cent of the patients (slight plus moderate). Thirty-three per cent of the PAS plus KI group had improved. After the second course of treatment the PAS group showed 31 per cent improvement against 28 per cent for the PAS plus KI group.

None of the patients evaluated showed any consistent conversion to sputum negative for tubercle bacilli. In this respect also there was no difference between the two groups, and virtually all patients continued to discharge bacilli.

COMMENT

In the dosage employed (1 gm. daily) potassium iodide given with PAS exerted no demonstrable harm in those patients with chronic fibrocavitary pulmonary tuberculosis. It does not necessarily follow that this would be true among patients with other forms of pulmonary tuberculosis. The lack of significant improvement provided no evidence that potassium iodide potentiates the effectiveness of PAS. It appears obvious that potassium iodide, in the dosage employed, with PAS has no demonstrable effect on the results obtained in this type of disease.

SUMMARY

A group of patients with chronic fibroid pulmonary tuberculosis was treated with PAS. A similar group of patients was treated with PAS plus potassium iodide, 1 gm. daily. Roentgenographic and bacteriologic evaluation of the results revealed no significant differences between the two groups. Potassium iodide appeared to have neither a harmful nor a helpful effect, in the dosage employed, on the course of this form of pulmonary tuberculosis.

SUMARIO

El Yoduro Potásico y el PAS en la Tuberculosis Fibrosa Crónica

Un grupo de enfermos con tuberculosis pulmonar fibrosa crónica fué tratado con PAS. Un grupo semejante fué tratado con PAS más yoduro de potasio diariamente. El estudio de los resultados a base de las radiografías y del esputo no reveló mayor diferencia entre los dos grupos. El efecto del yoduro de potasio no pareció ser ni nocivo ni útil.

RESUME

L'iodure de potassium et PAS dans la tuberculose fibreuse chronique

Un groupe de malades atteints de tuberculose pulmonaire fibreuse chronique a été traité par le PAS. Le PAS, plus de l'iodure de potassium, ont été administrés chaque jour à un deuxième groupe présentant des conditions similaires. Les résultats de l'examen radiologique et celui des crachats ne montraient aucune différence significative entre les deux groupes. L'iodure de potassium n'a paru avoir aucune action bonne ou mauvaise.

Acknowledgment

The writer is indebted to Drs. Eli Tigay and Vito Pisani for aid in the clinical management of the patients.

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THE GROWTH AND ENUMERATION OF MYCOBACTERIA IN TRANSPARENT AGAR MEDIUM[1]

DIRAN YEGIAN AND VERA BUDD

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INTRODUCTION

The introduction of liquid Tween-albumin medium (1) has demonstrated that tubercle bacilli multiply readily beneath the surface of liquid media. The literature does not reveal conclusive evidence, however, that any appreciable amount of subsurface growth can be obtained in a solid medium in the absence of increased oxygen tension. In view of this, it was considered of sufficient interest to investigate the possibility of obtaining subsurface growth of several strains of *Mycobacteria* in the solid transparent medium described by Dubos and Middlebrook (2).

The present report describes a procedure for the cultivation of *Mycobacteria* in deep culture in a solid transparent medium and at the same time provides a simple method for the enumeration of viable cells from suspensions of *Mycobacteria* or from pathologic material. The data include a comparison of colony counts obtained by surface plating and the pour-plate procedure, the diversity of colony morphology shown by different strains of *Mycobacteria*, and other biologic considerations of the deep colonies.

MATERIAL AND METHODS

Fifteen strains of *Mycobacteria* were used. Among these were organisms from cultures of *Mycobacterium tuberculosis*, H37Rv; the avirulent variant, H37Ra; and tubercle bacilli freshly isolated from sputum; two strains of BCG; *Mycobacterium tuberculosis*, avian type; *Mycobacterium ranae;* and a chromogenic acid-fast microorganism isolated from gastric washings. Streptomycin-sensitive, -resistant, and -dependent strains and a strain resistant to para-aminosalicylic acid were included as indicated in table 1. The sediment from a sputum rich in tubercle bacilli was also plated.

The solid medium employed had the following composition:

Basal Medium	
KH_2PO_4	1.0 gm.
$Na_2HPO_4 \cdot 12H_2O$	6.3 gm.
Asparagine	2.0 gm.
Additional Substances	
Distilled water	750 ml.
Tap water	200 ml.
Ferric ammonium citrate	0.05 gm.
Sodium citrate	0.13 gm.
$Mg\ SO_4 \cdot 7H_2O$	0.05 gm.

[1] From the Ray Brook Tuberculosis Hospital, Ray Brook, New York.

The pH was adjusted to 7.2; 1.5 per cent of agar (Difco) was added; and the medium was autoclaved. To each 900 ml. of medium, melted and cooled to 45° C., 100 ml. of oleic acid-albumin-glucose complex were added. The complex was prepared by dissolving 0.12 ml. of oleic acid in 10 ml. of N/20 NaOH by shaking with a rotary motion in a small flask. Five milliliters of this solution were added to 95 ml. of neutral 5 per cent solution of bovine plasma Fraction V in physiologic salt solution containing 5 per cent glucose. The material was sterilized by filtration (Seitz).

TABLE 1

Colony Counts by Pour-Plate and Surface-Growth Procedures

STRAIN OF *Mycobacterium*	AVERAGE NUMBER OF COLONIES PER PLATE		
	10^{-7} surface	10^{-7} poured	10^{-6} poured
M. tuberculosis, strain H37Rv, SM-sensitive	14.0	16.0	132.0
M. tuberculosis, strain H37Rv, SM-resistant	21.2	25.4	205.0
M. tuberculosis, strain H37Rv, SM-dependent	23.4	24.6	229.0
M. tuberculosis, strain H37Rv, PAS-resistant	10.0	12.8	131.0
M. tuberculosis, isolated from sputum, SM-sensitive	11.2	15.0	126.4
M. tuberculosis, isolated from sputum, SM-resistant (1)	5.0	5.2	50.0
M. tuberculosis, isolated from sputum, SM-resistant (2)	7.6	8.2	78.0
Concentrated sediment from a highly positive sputum*	92.4	92.2	Too numerous to count accurately
M. tuberculosis, strain H37Ra	50.2	60.6	Too numerous to count accurately
M. tuberculosis, avian type	53.0	63.6	Too numerous to count accurately
BCG—Phipps Institute strain	12.0	17.4	111.0
BCG—Albany strain	3.4	9.2	68.2
M. ranae, SM-sensitive	21.0	29.0	233.0
M. ranae, SM-resistant	34.4	47.6	425.0
Chromogenic acid-fast	22.6	23.0	226.0

* Sputum dilutions were 10^{-4} and 10^{-5} instead of 10^{-6} and 10^{-7}.

The composition of this medium is slightly modified from the original. It should be mentioned that certain lots of agar give a granular precipitate which interferes with the transparency of the medium. In this event, the hot medium may be filtered through a Buchner filter using a special filter paper designed for filtering culture media and viscous fluids.

Liquid Tween-albumin cultures of *Mycobacteria* were thoroughly shaken and diluted to 10^{-6} and 10^{-7} in 0.1 per cent albumin in distilled water (3) using separate pipettes for each dilution. One-milliliter quantities of the 10^{-6} and 10^{-7} dilutions were placed in the bottom of a series of five Petri plates for each dilution, and approximately 25 ml. of melted and cooled oleic acid medium were poured into the plates which were rotated to ensure mixing of the inoculum. Five additional plates were poured, and when the medium had solidified each was inoculated on the surface with 1 ml. of the 10^{-7} dilution. The inoculum was spread by tilting the plates.

After incubation at 37°C. for forty-eight hours to permit evaporation of excess moisture, the plates were sealed with wide rubber bands and incubation was continued. The tubercle

bacilli were incubated for thirty to thirty-five days, and the more rapidly growing cultures for shorter periods.

RESULTS

The colony counts in table 1 provide a comparison of pour-plate and surface-plating methods for the enumeration of viable cells from cultures of *Mycobacteria*. In dilutions of 10^{-7}, the average number of colonies in the pour plates consistently

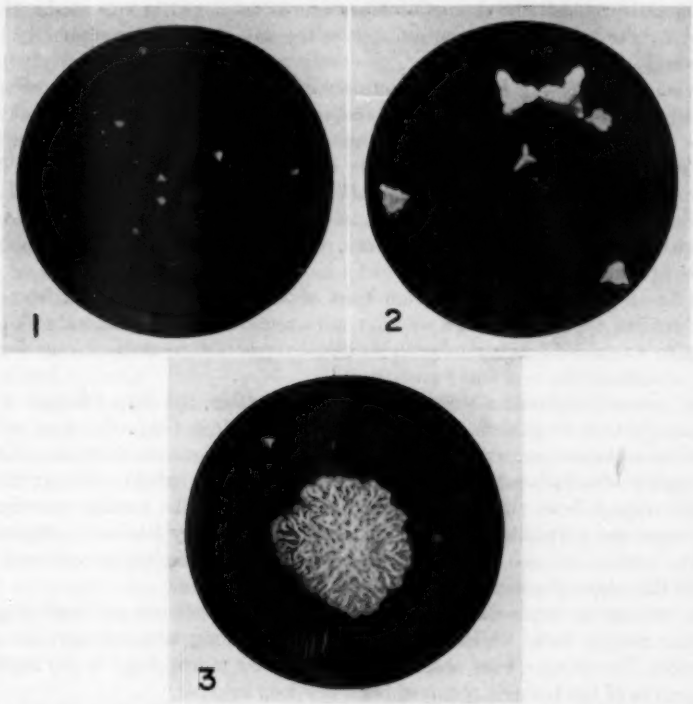

FIG. 1. Deep colonies of *M. tuberculosis*, strain H37Rv, incubated five weeks, showing irregular outline and variable morphology.

FIG. 2. Deep colonies of *M. tuberculosis*, strain H37Rv, incubated ten weeks, showing heaped-up appearance of colonies that pierce the surface of the medium.

FIG. 3. *M. ranae*, incubated eight days, showing large surface colony and two deep colonies. Photographs slightly enlarged.

exceeded the number of colonies grown by the surface-plating procedure. However, the average number of subsurface colonies from the 10^{-6} dilution, when corrected, is uniformly less than that from the corresponding 10^{-7} dilution. This can be explained by the fact that, in the dilution containing the higher concentration of bacterial cells, there is a greater probability of a colony

originating from more than a single cell because of the opportunity for clumping provided by the closer proximity of the cells to each other. This is what would be expected with any rapidly growing nonacid-fast microorganism if the number of bacteria in the inoculum was increased, and therefore tends to confirm the adaptability of *Mycobacteria* to this standard bacteriologic procedure.

During the period of microscopic growth the individual colony, when viewed under low power of the microscope, had a flat, round appearance which was characteristic of all the strains of *Mycobacteria* employed in this study. However, by the time colonies were visible to the naked eye, the morphology was extremely variable.

Mammalian tubercle bacilli: After thirty days of incubation the deep colonies usually attained a size of 0.5 mm. in diameter. The colonial morphology at this time or on further incubation was extremely variable, presumably as a result of the varying depth of the colonies in the medium. Some appeared scaly and flat; others, raised and rough. A few showed edges more serrated than lobulated and still others had the configuration of odd-shaped crystals. A number of colonies broke through the medium to the surface, and the subsequent growth was heaped up irregularly (figures 1 and 2).

Avian tubercle bacilli: The avian type of *M. tuberculosis* differed from the mammalian type in that the colonies were rounder and had smoother edges. Surface colonies of avian tubercle bacilli, in contrast to deep colonies, were flat, amoeboid-like and finely granular.

M. ranae: Examined after eight days of incubation, the deep colonies of *M. ranae* appeared irregular in outline with lobulated edges. On further incubation, the center became more dense and the edges myceloid or ramose. Some colonies emerged to the surface of the medium and subsequently spread, differing in this latter respect from the mammalian tubercle bacilli. The surface colonies of *M. ranae* were wrinkled, and the outline was irregularly lobulated (figure 3).

The surface colonies of the chromogenic acid-fast strain are smooth and flat while the deep colonies resemble those of the avian strain.

It should be emphasized that none of the deep colonies are lenticular in appearance, a form which is often observed among nonacid-fast bacterial colonies. No changes were observed in the cellular morphology or the staining properties of the bacteria obtained from the deep colonies.

DISCUSSION

The major purpose of this study was to determine whether tubercle bacilli, from cultures as well as from pathologic material, are capable of growth in the depth of the transparent solid medium described by Dubos and Middlebrook. It is evident from this experiment that tubercle bacilli can grow from a single cell or group of cells to form a colony of appreciable size in this medium. Apparently sufficient oxygen to support growth is present as a result of the limited amount in the medium and the entrance of atmospheric oxygen into the medium by diffusion. It is generally agreed that tubercle bacilli grow more rapidly in the presence of an ample supply of oxygen, but it is to be emphasized that this

microorganism does multiply even when the supply of oxygen is limited. This is of interest in relation to the statement by Dubos (4) "that any oxygen pressure compatible with the life of adult animal cells will be adequate, not only for the survival of tubercle bacilli, but also for their multiplication even though at a slow rate. Furthermore, some oxygen must reach the caseous material by diffusion and may be present in solution in its aqueous phase."

Comparison of the pour-plate and surface-plating methods showed a numerically greater colony growth in the former. This was most likely a consequence of the better dispersion of bacterial cells in the pour plates and also of the fact that the microorganisms were not in contact with the diluent for any significant length of time. In contrast, on the surface plates the cell suspension was exposed to the diluent for the time (almost forty-eight hours) required for its evaporation, and during this interval some cells probably died or were agglutinated.

The morphologic characteristics of the deep colonies were compared with those grown on the surface. To our knowledge this has not been previously described. No change was noted in the morphology and staining properties of cells obtained from the deep colonies.

The pour-plate procedure may be used to advantage in the selection of mutants from large bacterial populations, specifically the resistant organisms in a parent population sensitive to antibacterial agents. The better dispersions and multiple layers for growth permit a larger inoculum per plate, with obvious economy in time and material.

In regard to the practical use of the pour-plate method in the diagnostic laboratory, tubercle bacilli have been cultured by this method from sputum specimens which on concentration and smear examination revealed no acid-fast bacilli. In view of the much larger inoculum that can be employed in the pour plate, this method would appear to have an advantage over the conventional method for the cultivation of tubercle bacilli. Studies are being carried out to evaluate the procedure for routine laboratory purposes.

The introduction by Dubos and his associates of the liquid and solid media used in these studies merits emphasis as a definite advance in the application of the standard bacteriologic procedures to the study of *M. tuberculosis*.

SUMMARY

The cultivation of tubercle bacilli in the depths of a transparent agar medium has been described. This pour-plate procedure appears to have certain advantages over surface-plating methods for the enumeration of viable tubercle bacilli from cultures and pathologic material.

SUMARIO

El Crecimiento y Enumeración de las Micobacterias en Medio de Agar Transparente

Descríbese aquí el cultivo de bacilos tuberculosos en la profundidad de un medio de agar transparente. Este procedimiento en placa vertida parece poseer ciertas ventajas sobre las técnicas de siembra superficial en lo tocante a la

enumeración de bacilos tuberculosos viables en los cultivos y materias patológicas.

RESUME

Culture et dénombrement du Mycobacterium tuberculosis dans un milieu transparent à l'agar

La culture en profondeur du bacille tuberculeux dans un milieu transparent à l'agar a été décrite. Ce procédé de culture en boîte de Pétri paraît offrir des avantages sur les cultures en surface pour dénombrer les bacilles tuberculeux vivants dans les cultures et les produits pathologiques.

Acknowledgment

The authors are grateful to Mr. Joseph Kurung for the photographs.

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STREPTOMYCIN AND PAS IN EXPERIMENTAL TUBERCULOSIS OF GUINEA PIGS INFECTED INTRACEREBRALLY WITH VIRULENT TUBERCLE BACILLI[1, 2]

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In a previous publication (1) the preliminary results of the effect of streptomycin in experimental tuberculosis of guinea pigs infected intracerebrally with virulent H37Rv tubercle bacilli were presented. The present report is concerned with the final results of the preliminary experiment and with the results of streptomycin and para-aminosalicylic acid (PAS) treatment, alone and in combination, in a larger group of guinea pigs similarly infected.

EXPERIMENTAL

Preliminary Experiment

Twenty guinea pigs, weighing between 800 and 1,000 gm., were inoculated intracerebrally with 0.0001 mg. (dry weight) of H37Rv microorganisms through a small drill hole in the posterodorsal part of the skull, just to one side of the midline. The animals were under light ether anesthesia, and the organisms were introduced with a tuberculin syringe fitted with a one-quarter-inch No. 26 hypodermic needle. Streptomycin treatment was started immediately after infection in 10 of these animals. Eighteen milligrams of streptomycin were given daily in four divided doses by the intramuscular route for 21 days, after which the dose was doubled so that the animals received 36 mg. per day. After fifty-eight days of streptomycin, therapy was discontinued in 4 of the guinea pigs.

The results of this experiment were briefly as follows: Nine of the untreated animals died between the seventeenth and twenty-second days after infection. One animal lived for 92 days. None of the treated guinea pigs died during this period. Neurologic signs, consisting of paralysis of the hindquarters, loss of equilibrium, and convulsions upon stimulation, were evident during the third week. Many of the streptomycin-treated animals also exhibited these neurologic signs, but after the dose of the drug was increased to 36 mg. per day they disappeared. All of the animals deprived of streptomycin after 58 days of treatment demonstrated a return of paralysis of the hindquarters, and all of the 4 died 40 to 74 days after treatment was stopped. The remaining 4 guinea pigs were continued on streptomycin treatment, the dosage being changed after the seventy-second day to 10 mg. twice daily. Three of these animals died on the three hundred and sixteenth, three hundred and fifty-ninth, and four hundred and forty-fifth days, respectively, after infection, and the fourth was killed on the seven hundred and fortieth day.

Pathologic and bacteriologic studies: At the time of autopsy the brain was divided in half, one part being fixed in formalin for microscopic study, and the other ground up and prepared for culture of tubercle bacilli. In each case, the brain was cultured on tubes of American Trudeau Society solid medium containing graded concentrations of streptomycin, as well as on control tubes without streptomycin, so that a direct streptomycin-sensitivity test was done. All positive cultures were subcultured in Tween-albumin liquid medium and tested in the same liquid medium containing graded concentrations of streptomycin. The

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[1] From the Trudeau Laboratory of the Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

[2] This study was aided by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service.

TABLE 1

Results of Preliminary Experiment. Guinea Pigs Infected Intracerebrally; Treatment with Streptomycin Started Immediately

GUINEA PIG NUMBER	DAYS OF LIFE	DAYS OF STREPTOMYCIN TREATMENT	PARAPLEGIA	MICROSCOPIC BRAIN FINDINGS[a]				CULTURES FOR TUBERCLE BACILLI	STREPTOMYCIN SENSITIVITY	OTHER LESIONS
				Lymphocytic Meningeal Infiltration	Epithelioid Tubercles	Caseation	Hydrocephalus			
356	17	0		+++	Brain	Brain	0			0
389	18	0		+++	Meninges and brain	Brain	0			0
393	19	0		++	0	Meninges	0			0
375	19	0		++	Meninges and brain	Meninges	0			0
366	19	0		++	Meninges and brain	Meninges	0			0
362	19	0		++	Meninges	Meninges	0			0
354	21	0		++	Meninges	0	0			Spleen ±, few acid-fast bacilli on smear
395	21	0		++	Meninges	0	0			0
394	22	0		++	Meninges and brain	Brain	0			0
360	92	0	Yes	0	Meninges and brain	Meninges and brain	0			Advanced tuberculosis of lungs, liver, and spleen

399	5	5		±	0	0	0			Died of intercurrent infection
382	10	10		+	0	0	0			Died of intercurrent infection
358	98†	58	Yes	+	0	0	+			0
332	109†	58	Yes	+	0	0	++			0
392	127†	58	Yes	+	Meninges	Meninges	+++			Few small tubercles—lungs
376	132†	58	Yes	+	Meninges and brain	Meninges	+++			Disseminated tuberculosis of spleen, hepatic and inguinal lymph nodes
380	316	316	Yes	?	0	0	++	Brain—positive	Sensitive	0
330	359	359	Yes	++	0	0	?‡	Brain—positive	Sensitive	Far advanced tuberculosis of lungs, liver, and spleen
								Lung—positive	Highly resistant	
								Liver—positive	Highly resistant	
								Spleen—positive	Highly resistant	
								Inguinal node—positive	Highly resistant	
257	445	445	No	—	—	—	—	Brain—negative		Chronic type of tuberculosis of lungs, liver, and spleen; pleural and peritoneal fluid
								Lung—positive	1–2.5‖	
								Spleen—positive	125–250	
								Lymph node—positive	125–250	
371	740 K§	740	Progressive weakness	+	0	0	+++	Brain—negative		0

* Graded on scale of 0 to +++

† Treatment discontinued after 58 days, after which this group of 4 animals lived an average of 58 days.

‡ Specimen fragmented.

§ This animal was killed. The others died spontaneously.

‖ Resistant to 1, sensitive to 2.5 γ per cc. of liquid Tween-albumin medium.

pathologic findings are presented in table 1 and will be discussed in conjunction with the main experiment.

Second Experiment

Fifty tuberculin-negative guinea pigs (average weight, 500 gm.) were infected in the same manner with the same strain as in the first experiment. Four animals died within 5 days and are therefore not included in the results. Death of these animals was attributed to hemorrhage and trauma to the brain substance incident to the procedure of making the drill hole in the skull. Antimicrobial therapy was again started immediately after infection. The guinea pigs were grouped as follows:

Group 1. Nine guinea pigs; untreated controls.

Group 2. Nine guinea pigs; treated with PAS alone, 200 mg. twice daily, until death.

Group 3. Five guinea pigs; treated with streptomycin, 10 mg. twice daily for 147 days.

Group 4. Five guinea pigs; treated with streptomycin, 10 mg. twice daily, plus PAS, 150 to 200 mg. twice daily for 147 days.

Group 5. Four guinea pigs; treated with streptomycin plus PAS, in the same dosage as *Group 4*, for 147 days, then with streptomycin alone until death.

Group 6. Fourteen guinea pigs; treated with streptomycin alone continuously until death, 20 mg. twice daily for 147 days, then 15 mg. once daily.

The PAS[3] was given by mouth in the form of a solution of the neutralized acid through a tuberculin syringe and blunt needle. The streptomycin[4] was given intramuscularly.

RESULTS

As in the preliminary experiment, the control animals began to show abnormal neurologic signs approximately two weeks after infection. Disturbances of equilibrium and intermittent convulsions were most prominent. All of the control animals (*Group 1*) were dead by the twenty-third day, the average survival time being 16 days.

The animals treated with PAS alone (*Group 2*) behaved exactly like the untreated animals. All were dead by the twenty-sixth day, with an average survival time of 20 days.

All of the animals receiving streptomycin treatment remained free of neurologic signs during the early course of the infection. Two of the animals treated with the lower dosage of streptomycin (1 in *Group 3* and 1 in *Group 4*) died 30 days after infection without exhibiting neurologic signs. The other 8 animals in *Groups 3* and *4*, which were treated for 147 days only, survived throughout the period of treatment. After antimicrobial therapy was discontinued, however, those treated with streptomycin alone succumbed in 22 to 43 days, and those treated with streptomycin and PAS died within a period of 19 to 36 days.

[3] *p*-Aminosalicylic acid (Pamisyl) was kindly supplied by Parke, Davis & Co., Detroit, Michigan.

[4] Streptomycin sulfate manufactured by Charles Pfizer and Co.

Of the 18 animals in *Groups 5* and *6* which were treated without interruption, 8 survived for 450 days and were then sacrificed, while 10 died during treatment (2 of unrelated secondary infections). Most of the animals which succumbed 90 or more days after infection exhibited a progressive paralysis of the hindquarters for a week or two before death. Brains of these guinea pigs nearly always showed a definite hydrocephalus. In table 2 are indicated the principal findings in the guinea pigs of the second experiment.

The gross and microscopic pathology and the results of bacteriologic studies in the two experiments will be considered together.

Gross Pathology

The control animals which died between 12 and 17 days after infection showed injection of the vessels over the surface of the brain with a bare trace of gray exudate. Smears from the surface of the brain revealed many acid-fast bacilli. After the eighteenth day the exudate was more pronounced, and many acid-fast bacilli could still be seen on smear. After 21 days, enlargement of the cervical nodes became evident; and after the twenty-sixth day, caseation was seen in these cervical nodes. The animals treated with PAS alone revealed essentially the same findings. The 2 animals that died on the thirtieth day (No. A-2, treated with streptomycin; and No. 949, treated with streptomycin and PAS) had enlarged cervical nodes with tiny caseous centers. Smears of the surface of the brain showed a few acid-fast bacilli, although there was no exudate visible in either case.

The animals which died after having received adequate streptomycin therapy showed nothing grossly abnormal on the surface of the brain, and smears from the surface were negative for acid-fast bacilli. Lesions of tuberculosis were seen in the lymph nodes and other visceral organs in many of the guinea pigs in which therapy had been discontinued, but usually not in the animals maintained on streptomycin treatment. Guinea pig No. A-11, killed after 450 days of continuous treatment with streptomycin, showed enlargement of a cervical node (one epithelioid tubercle seen microscopically) and one nodular tuberculous lesion in the spleen. Guinea pigs No. 330 and No. 357 in the first experiment both died with far advanced tuberculous lesions throughout the body and yielded tubercle bacilli highly resistant to streptomycin on culture of some of their organs. This phenomenon will be discussed more fully in the section on bacteriology.

Histopathology

The early lesions seen in the brains and meninges of the untreated guinea pigs were generally of a nonspecific nature. In the animals which died within the first two weeks after infection, only a diffuse lymphocytic infiltration was seen throughout the meninges. This was usually most pronounced at the base of the brain in the region of the optic chiasm. Slight extension of the lymphocytic reaction into the cerebral tissue along the vessels was common. The ventricular lining and choroid plexuses were free of reaction. The lesions at the site of inocu-

TABLE 2

Results of Second Experiment. Guinea Pigs Infected Intracerebrally; Antimicrobial Therapy Started Immediately

GUINEA PIG NUMBER	DAYS OF LIFE	DAYS OF TREATMENT	PARAPLEGIA	MICROSCOPIC BRAIN FINDINGS*				CULTURES FOR TUBERCLE BACILLI	STREPTOMYCIN SENSITIVITY	OTHER LESIONS
				Lymphocytic Meningeal Infiltration	Epithelioid Tubercles	Caseation	Hydrocephalus			
Group 1 9 pigs	12–23 Average 16	0		+++	Meninges and brain	Meninges	0			0
Group 2 9 pigs	17–26 Average 20	PAS 200 mg. 2× day per os		+++	Meninges and brain	Meninges	0			0
Group 3 A2	30	SM 10 mg. 2× day intramuscularly for 147 days	0	+	0	0	0			Enlarged cervical nodes
A1	169		Yes	+	0	0	+++	Brain—negative		0
A5	169		Yes	+	0	0	++	Brain—negative		0
A7	185		0	+	0	0	+++	Brain—negative		0
A9	190		Yes	+	Brain	Brain	?†	Brain—positive	Sensitive	Tubercles in cervical node and spleen
Group 4 949	30	SM 10 mg. 2× day intramuscularly plus PAS 150–200 mg. 2× day per os for 147 days	0	++	0	0	?			Enlarged cervical nodes
A20	166		Yes	+	0	0	++	Brain—negative Spleen—positive Lung—positive	 Sensitive Sensitive	Tubercles in spleen and cervical nodes

A10	166		0	+	Meninges	0	?	Brain—positive	Sensitive	Enlarged cervical and tracheobronchial nodes
951	177		Yes	+	0	Meninges	++			Enlarged inguinal nodes
946	183		Yes	+	0	Meninges	+	Brain—negative Cervical node—positive	Sensitive	Cervical, hepatic, and inguinal nodes, large and hard
Group 5										
958	154	SM + PAS for 147	0	++	0	0	?			Pneumonia
947	339	days; then SM	0	+	0	0	++	Brain—negative		0
963	347	alone until	Yes	+	0	0	+++			0
956	450 K‡	death.	0	+	0	0	±			0
Group 6										
A15	86	SM alone continuously until	0	+	0	0	?			Pneumonia
A17	96	death, 20 mg.	Yes	++	0	0	+++			0
A53	180	2× day for 147	Yes	+	0	0	+++	Brain—negative		0
A60	219	days, then 15	Yes	+	0	0	?	Brain—negative		0
A 8	336	mg. 1× day in-	0	++	0	0	?	Brain—negative		0
A18	386	tramuscularly	Yes	+	0	0	+			0
A57	397		Yes	+	0	0	±			0
A11	450 K‡		0	+	0	0	0			1 microscopic tubercle in cervical node; 1 nodular tubercle in spleen
A12	450 K		0	+	0	0	±			0
A13	450 K		0	+	0	0	0			0
A14	450 K		0	+	0	0	0			0
A16	450 K		0	+	0	0	0			0
A19	450 K		0	+	0	0	±			0
A56	450 K		Yes	+	0	0	++			0

* Graded on scale of 0 to +++. † Specimen fragmented. ‡ Killed.

lation indicated that the microorganisms had been placed within the cerebral tissue since it was only in that location that distortion of the cerebral tissue was seen.

In the animals which died 19 or more days after infection, the reaction had become characteristically tuberculous. Epithelioid cells, giant cells, and caseation were present in the meninges in addition to the diffuse lymphocytic infiltration. In guinea pig No. 360, which died 92 days after infection, a caseous abscess, 1 cm. in diameter, was present at the site of inoculation, and the meninges were free of diffuse lymphocytic infiltration.

The lesions in the animals treated with PAS were essentially the same as in the untreated control animals.

Few of the streptomycin-treated animals were examined at a period comparable with that for the control and PAS-treated groups. The 2 animals which died soon after infection (No. 399 and No. 382, which survived 5 and 10 days, respectively) showed the beginning of the diffuse infiltration of lymphocytes in the meninges. Number A-2, which died after 30 days, showed only a slight lymphocytic meningeal infiltration; and No. 949, which died on the same day, demonstrated a more pronounced infiltration of lymphocytes in the meninges.

Most of the streptomycin-treated animals which died three months or more after infection exhibited a progressive paralysis of the hindquarters for a week or two before death. External examination of these brains revealed no abnormalities. When they were sectioned after fixation, it was noted that the cerebral ventricles were distinctly dilated, and in some instances the cerebral tissue was considerably reduced in amount. Microscopically, the presence of hydrocephalus was confirmed. Examination of the meninges in these animals revealed only a very slight lymphocytic infiltration, usually much less pronounced than that in the controls which had died earlier. Epithelioid cells and caseation were not seen except in those animals in which therapy had been discontinued for a period before death. Most of the guinea pigs which had been taken off streptomycin treatment (after 58 days in the first experiment, and after 147 days in the second experiment) demonstrated a definite hydrocephalus at death.

Eight guinea pigs were killed after 450 days of continuous streptomycin therapy, and all revealed the presence of a slight lymphocytic infiltration of the meninges; but the ependyma and choroid plexuses were free of lesions. No epithelioid tubercles or caseation were seen in the meninges or the brains. Only one of these animals exhibited a definite hydrocephalus. The one guinea pig in the first experiment which was sacrificed after 740 days of treatment demonstrated a pronounced hydrocephalus.

Typical sections of treated and untreated animals are shown in Plates I and II.

Bacteriology

It may be seen in tables 1 and 2 that cultures were obtained from the brains of 8 guinea pigs which had been treated with streptomycin up to the time of death. Only 2 of these cultures were positive for *M. tuberculosis*. One of the

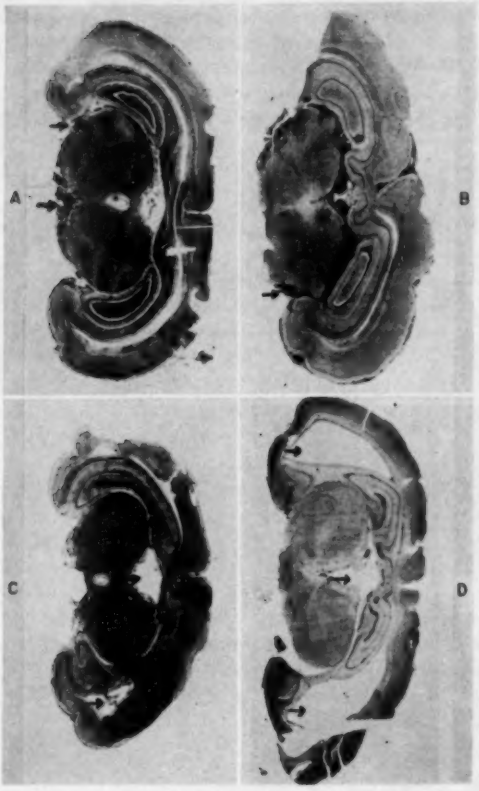

PLATE I

Cross-sections through cerebral hemispheres and brain stem. Magnification approximately 3 ×. (Arrows denote points of emphasis.)

A. Untreated control, guinea pig No. 366, died 19 days after infection. Meninges are thickened, especially over the base of the brain stem and between the stem and the lower tip of the hemispheres. The crescent-shaped lateral ventricles are of normal size.

B. Guinea pig No. A-26, treated with PAS alone, died 19 days after infection. Similar to A.

C. Guinea pig No. A-19, treated with streptomycin continuously for 15 months before sacrifice. The meninges are delicate and appear normal at this magnification. The lateral ventricle on the right and the third ventricle (center) are possibly somewhat dilated.

D. Guinea pig No. A-1, treated with streptomycin for 147 days, developed paraplegia and died 22 days later. The meninges are delicate. Pronounced hydrocephalus is present, with dilatation of both lateral ventricles and the third ventricle.

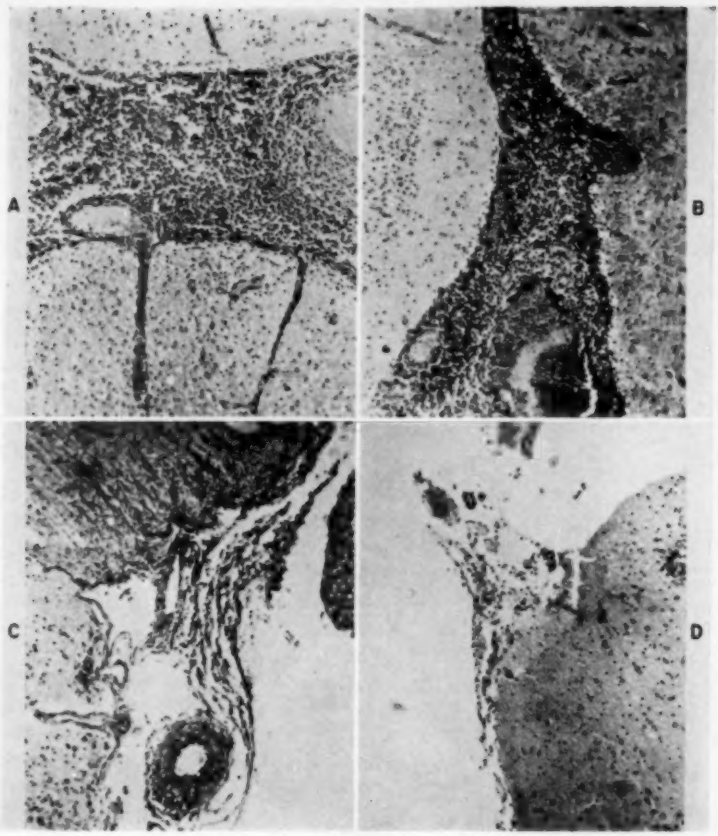

PLATE II

Higher magnification (70 ×) of lesions from same brains as in plate 1, showing area of meninges between tip of cerebral hemisphere and the brain stem.

A. Untreated control No. 366. There is dense infiltration by lymphocytes and macrophages. Acid-fast bacilli can be demonstrated in this area, although the tissue reaction is not typically tuberculous.

B. No. A-26, PAS-treated. The reaction is similar to that demonstrated by No. 366. An early epithelioid cell tubercle is also shown.

C. No. A-19, streptomycin-treated for 15 months. There is only slight thickening and lymphocytic infiltration in the meninges, with no typically tuberculous lesions to be seen.

D. No. A-1, streptomycin-treated for 147 days, died 22 days later. Very slight diffuse lymphocytic infiltration of the meninges.

positive cultures was from guinea pig No. 380, which had been treated with streptomycin continuously for 316 days and was paraplegic and hydrocephalic at death. The tubercle bacilli obtained were sensitive to streptomycin. The other guinea pig (No. 330) died of far advanced generalized tuberculosis. Tubercle bacilli obtained from the lung, liver, spleen, and inguinal node were highly resistant to streptomycin, whereas those obtained from the brain were still sensitive.

Guinea pig No. 357 also yielded tubercle bacilli highly resistant to streptomycin from the spleen and a lymph node although organisms obtained from the lung showed only a very slight increase in resistance and cultures from the brain were negative.

The 2 guinea pigs yielding drug-resistant tubercle bacilli were treated with streptomycin at a time when other animals infected with streptomycin-resistant organisms were undergoing treatment by means of the same tuberculin syringe and needle. It cannot be definitely established whether the resistant organisms arose from the originally sensitive ones inoculated into the brain or whether they were introduced from the outside. From the distribution of the resistant organisms, the latter sequence of events seems more probable.

Treatment with streptomycin alone, as well as with the combination of streptomycin and PAS for 147 days, obviously did not sterilize the brains of these guinea pigs, for many of the brains yielded positive cultures when the animals died some time after treatment was discontinued.

DISCUSSION

Other than the observation that streptomycin was able to control a highly lethal experimental tuberculous meningitis in contrast to the lack of beneficial effect of PAS, the most significant finding in these experiments is the production of hydrocephalus and the relationship between this process and the late paraplegic deaths.

The literature concerning antimicrobial therapy of experimentally produced tuberculous meningitis is very limited. Luzzatto (2, 3) obtained results similar to those reported here, but he does not mention the finding of hydrocephalus despite the fact that one of his guinea pigs under streptomycin therapy lived for as long as 91 days after infection. In the present experiments, a marked hydrocephalus was seen in a guinea pig which died 96 days after infection. Levaditi and his associates (4) reported the production of hydrocephalus in mice infected intracerebrally with virulent tubercle bacilli. These investigators state that the ventricular dilation was seen principally in streptomycin-treated mice which survived a long time.

In the present experiments hydrocephalus was seen only in the animals treated with streptomycin. With one exception, the untreated animals did not live long enough for dilatation of the ventricles to become evident even if conditions favorable to its development were present. The one exception, guinea pig No. 360, lived for 92 days after infection, but showed no sign of hydrocephalus. In this animal, a large caseous abscess at the site of inoculation in the top of the brain was produced which, unaccountably, did not extend into the meninges. On the

other hand, guinea pig No. A-17 demonstrated a marked dilatation of the ventricles when it died after 96 days of streptomycin treatment. All of the 4 animals in the first experiment which were treated with streptomycin for only 58 days had hydrocephalus when they succumbed after therapy was discontinued, the 2 which lived the longest showing the greatest degree of dilatation. Most of the animals which died during streptomycin treatment evidently did so because of the paralysis associated with the hydrocephalus. Of the 8 animals in the second experiment which survived 450 days of streptomycin treatment, only one showed the presence of definite hydrocephalus. This animal, No. A-56, was also the only one of this group which had paralysis.

There was no evidence obtained in the present experiments which would indicate the exact cause of the hydrocephalus. Neither blockage of the foramena nor obstruction of the basal subarachnoid space was apparent. There was very little evidence of scar formation in the meninges in any of these animals. De (5) states that he has produced internal hydrocephalus in guinea pigs by introducing tubercle bacilli into the cisterna magna without streptomycin therapy. He believes that internal hydrocephalus in tuberculous meningitis is due to the obstruction of the basal subarachnoid by the tuberculous exudate independent of streptomycin treatment.

Treatment with PAS was entirely devoid of beneficial results. The addition of PAS to therapy with streptomycin for 147 days did not influence the relapse rate after treatment was stopped. After cessation of therapy those animals treated with streptomycin alone died in 22 to 43 days, while those treated with the combination of drugs died in 19 to 36 days.

These findings are in accord with the poor results reported with PAS therapy of tuberculous meningitis in humans. It may be postulated that the drug does not reach the brain in adequate concentration, or that it just is not a powerful enough antimicrobial agent to affect this type of disease. A third possibility is that the brain harbors a substance or substances which interfere with the action of PAS. There is very little information to indicate which factors are operative, except that Way and his co-workers (6) found relatively little PAS in the brain tissue of rats after a large intravenous dose of the drug.

Treatment with streptomycin begun immediately after infection and continued for 147 days obviously did not sterilize the brain and meninges. The causes of death in those animals in which the infection was allowed to relapse were of interest. The 2 animals which died early, after only 58 days of treatment, showed no cause of death except the hydrocephalus. The 2 which lived longer, however, had active, progressive tuberculosis in many organs of the body, in addition to a marked hydrocephalus.

The animals treated for 147 days and then allowed to go untreated until death presented essentially the same changes as the animals treated for the shorter period. Some which died early revealed nothing but marked hydrocephalus; whereas those which lived a little longer showed active, spreading tuberculosis throughout the body, as well as in the cranium. It is also interesting that a slight but definite infiltration of lymphocytes in the meninges persisted, despite prolonged streptomycin therapy. Even the guinea pig treated continuously for 740 days revealed this infiltration microscopically.

SUMMARY

Guinea pigs were infected intracerebrally with a small inoculum of virulent human tubercle bacilli (strain H37Rv). Some were kept as untreated controls; others were started on therapy immediately with different dosages of streptomycin alone, PAS alone, and the combination of streptomycin and PAS. Gross and microscopic examinations were made of the brains as well as of any other lesions in the body suspected of being tuberculous. Cultures of the organs for tubercle bacilli were made, and all isolated organisms were tested for sensitivity to streptomycin.

The untreated control animals began to show neurologic signs two weeks after infection, and all but one were dead within 22 days. The group of animals treated with PAS alone behaved exactly as the untreated group. Microscopic study revealed epithelioid tubercles and caseation in the meninges and in the brains as well as a diffuse lymphocytic infiltration in the meninges.

The guinea pigs treated daily with 18 mg. of streptomycin showed the onset of neurologic signs in the third week, but these were controlled by doubling the dose of streptomycin. The guinea pigs in the second experiment, treated with 10 and 20 mg. of streptomycin twice daily, failed to show these neurologic signs early in the experiment, and most of them remained alive for a long period of time.

In guinea pigs in which streptomycin therapy was discontinued after 58 or 147 days, the infection relapsed and all died within 74 days. The addition of PAS to the streptomycin treatment in animals treated for 147 days did not affect the relapse rate.

Those animals treated with streptomycin continuously remained entirely well for three months after infection. After this period, an occasional animal would show a progressive paralysis of the hindquarters, usually ending in death in two or three weeks. Specific tuberculous lesions in these animals were usually lacking; the only findings were a slight, diffuse lymphocytic meningeal infiltration and a dilatation of the ventricles of the brain.

Eight animals treated with streptomycin continuously remained alive 450 days after infection and were sacrificed. With one exception, they showed no abnormal lesions in the brain except a slight, diffuse lymphocytic meningeal infiltration. One animal, in addition, showed a definite hydrocephalus. One animal in the first experiment survived for 740 days of continuous streptomycin therapy. Culture of its brain was negative, but there was marked dilatation of the ventricles.

SUMARIO

La Estreptomicina y el PAS en la Tuberculosis Experimental de los Cobayos Infectados Intracerebralmente con Bacilos Tuberculosos Virulentos

Infectóse intracerebralmente a cobayos con un pequeño inóculo de bacilos tuberculosos humanos virulentos (cepa H37Rv). Algunos fueron retenidos como testigos no tratados, en tanto que en otros se inició inmediatamente una terapéutica con diferentes dosificaciones de estreptomicina sola, PAS solo o una combinación de estreptomicina y PAS. Hiciéronse exámenes macro- y micros-

cópicos de los cerebros, así como de todas las demás lesiones del cuerpo que parecían tuberculosas. También se hicieron cultivos de los órganos en busca de bacilos tuberculosos y se comprobaron todos los microbios aislados en cuanto a sensibilidad a la estreptomicina.

Los testigos no tratados comenzaron a mostrar signos neurológicos al cabo de dos semanas, y todos, menos uno, ya habían muerto a los veintidós días de la infección. El grupo de animales tratado con PAS solo se comportó exactamente como el grupo testigo. El estudio microscópico reveló tubérculos epitelioideos y caseación en las meninges y el cerebro así como infiltración linfocitaria difusa en las meninges.

Los cobayos tratados con 18 mg. de estreptomicina diariamente mostraron en la tercera semana iniciación de los signos neurológicos, pero éstos fueron cohibidos doblando la dosis de estreptomicina. Los cobayos del segundo experimento, tratados con 10 y 20 mg. de estreptomicina, dos veces diarias, evadieron los signos neurológicos al principio del experimento, y la mayor parte permanecieron vivos durante un período prolongado de tiempo.

Todos los cobayos en que se discontinuó la estreptomicinoterapia al cabo de 58 ó 147 días recidivaron y murieron em término de 74 días. La adición de PAS a la estreptomicinoterapia en los animales tratados por espacio de 147 días no afectó el índice de recidivas.

Los animales tratados con estreptomicina continuamente permanecieron absolutamente bien durante tres meses. Al cabo de dicho tiempo, alguno que otro animal reveló parálisis progresiva de las patas traseras, culminando por lo general en la muerte en dos o tres semanas. En esos animales solían faltar lesiones tuberculosas específicas, consistiendo los únicos hallazgos en leve infiltración linfocitaria difusa de las meninges y dilatación de los ventrículos cerebrales.

Ocho animales tratados continuamente con estreptomicina permanecían vivos 450 días después de la infección, cuando se les sacrificó. Con una excepción, no revelaban lesiones anómalas en el cerebro, aparte de leve infiltración linfocitaria difusa de las meninges. Un animal mostró además hidrocefalia bien definida. Un animal del primer experimento sobrevivió 740 días de continua estreptomicinoterapia. El cultivo cerebral fué negativo, pero había marcada dilatación de los ventrículos.

RESUME

La streptomycine et le PAS dans la tuberculose expérimentale du cobaye par inoculation intracérébrale de bacilles tuberculeux virulents

Des cobayes ont été inoculés intracérébralement avec une petite dose de bacille tuberculeux humain virulent (souches H37Rv). Certains ont été conservés comme témoins non-traités, les autres ont été soumis immédiatement au traitement; diverses doses de streptomycine seule, de PAS seul, de streptomycine en association avec le PAS ont été expérimentées. Il a été procédé à l'éxamen macro et microscopique du serveau ainsi qu'à celui de toute autre lésion suspectée d'origine tuberculeuse. Des cultures d'organes pour la recherche du bacille tuberculeux ont été effectuées et tous les bacilles isolés ont été soumis à l'épreuve de la sensibilité à la streptomycine.

Les témoins non traités ont commencé à montrer des signes neurologiques au bout de deux semaines; tous, sauf un, ont succombé 22 jours après l'inoculation. Le groupe d'animaux traités par le PAS seul s'est comporté exactement comme le groupe de contrôle. L'examen histologique a révélé la présence de tubercules épithélioides et de caséification dans les méninges et le cerveau, ainsi qu'une infiltration lymphocytaire diffuse.

Les cobayes qui avaient été traités avec 18 mg de streptomycine par jour ont présenté un début de signes neurologiques au cours de la troisième semaine, mais ces manifestations ont été contrôlées en doublant la dose de streptomycine. Les cobayes de la deuxième expérimentation traités avec 10 et 20 g. de streptomycine deux fois par jour ont échappé aux manifestations neurologiques du début de l'expérimentation et la plupart d'entre eux ont survécu pendant très longtemps.

Les cobayes, chez lesquels la streptomycinothérapie avait été interrompue au bout de 58 ou de 147 jours, ont eu des rechutes et ils ont succombé dans les 74 jours. L'adjonction de PAS à la streptomycine chez les animaux traités pendant 147 jours n'a pas modifié le taux des rechutes.

Ceux des animaux ayant été traités d'une manière continue par la streptomycine se sont maintenus en très bon état pendant trois mois. A partir de ce moment on a observé de temps en temps chez un des animaux une paralysie progressive du train arrière, qui se terminait habituellement par la mort au bout de 2 ou 3 semaines. Les lésions tuberculeuses spécifiques manquaient habituellement chez ces animaux, les seules manifestations observées étaient une légère infiltration lymphocytaire diffuse des méninges et une dilatation des ventricules cérébraux.

Huit animaux traités d'une manière continue par la streptomycine étaient encore vivants 450 jours après l'inoculation et ont été sacrifiés. A l'exception d'un seul, il n'a pas été observé de lésion anormale dans le cerveau sauf une légère infiltration lymphocytaire diffuse des méninges. Un des animaux présentait une véritable hydrocéphalie. Un des animaux de la prmière expérimentation, soumis à la streptomycinothérapie continue, a survécu pendant 740 jours; des cultures de ses tissus cérébraux se sont montrées négatives mail il existait une dilatation marquée des ventricules.

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SULFONE COMPOUNDS AND POTASSIUM IODIDE ALONE AND IN COMBINATION WITH STREPTOMYCIN IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS OF GUINEA PIGS[1, 2]

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INTRODUCTION

At the time of the discovery of the therapeutic effectiveness of streptomycin in the treatment of tuberculosis, such derivatives of diaminodiphenylsulfone as Promin, Diasone, and Promizole were commanding considerable interest in the chemotherapy of the disease. Since then these compounds have been found inferior to streptomycin in the treatment of experimental tuberculosis of guinea pigs, rabbits, and rats and of tuberculosis of human beings. Nevertheless, the matter of administering a sulfone or other compound along with streptomycin for possible synergistic or additive chemotherapeutic effect is not without interest and possible importance, in view of the encouraging results obtained by the use of other drugs, notably para-aminosalicylic acid (PAS) in conjunction with streptomycin.

That sulfone compounds exert an impressive therapeutic effect upon the course of experimental tuberculosis is well established (1–7). Human beings, however, do not tolerate Promin and Diasone as well as guinea pigs when orally administered in doses sufficient to maintain adequate blood concentrations. Moreover, these compounds may produce hemolytic and progressive hypochromic normocytic anemias of varying severity in humans. Promizole is much less hemolytic and better tolerated but may produce reversible parenchymatous hyperplasia of the thyroid gland in the lower animals (8) and in children (9). The hyperplasia is apparently a consequence of hypothyroidism resulting from failure in the synthesis of thyroxin. Sulphetrone is also much less hemolytic than Promin but likewise may produce mild degrees of hemolytic and progressive hypochromic normocytic anemia in humans although it does not appear to be goitrogenic (10–12).

As it is now well established that Promin, Diasone, Promizole, Sulphetrone, and other derivatives of diaminodiphenylsulfone act synergistically or additively with streptomycin in the treatment of experimental tuberculosis (13–18), the question arises whether these enhanced therapeutic effects might not be attainable with nontoxic doses of the sulfones. Furthermore, their therapeutic effectiveness, alone or in combination with streptomycin, continues to encourage further efforts in the synthesis of newer sulfone and other compounds with the

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hope of discovering compounds of greater therapeutic activity and lesser toxicity in the treatment of tuberculosis in humans. Madigan and his colleagues (19) have reported that the combination of Sulphetrone and streptomycin is effective in the treatment of tuberculosis in humans. Likewise, Lincoln and her associates (20) have reported favorably on the combined treatment with Promizole and streptomycin of tuberculous meningitis of children; and Faget and Erickson (21) have found sulfone compounds alone to be effective in the treatment of leprosy.

Although Woody and Avery (22) have reported that potassium iodide showed no synergistic or additive effects with streptomycin on tubercle bacilli *in vitro* and but slight effects when administered alone in the treatment of experimental tuberculosis of guinea pigs, combination treatment with potassium iodide and streptomycin showed distinct synergistic or additive effects. In view of these results and since it has been found in this laboratory that iodide acts synergistically or additively with penicillin in the treatment of acute syphilitic orchitis of rabbits (23, 24), the administration of potassium iodide alone and in combination with streptomycin has been included in the present investigation. In 1914, Jobling and Petersen (25) reported that iodine combines with unsaturated fatty acids and neutralizes their ferment-inhibiting properties, with the result that ferment activity develops within areas of caseation with liberation of tubercle bacilli in the sputum. They also stated that iodine might serve another purpose by facilitating solution and absorption of caseous material, thus exposing the bacilli, which otherwise might be inaccessible to effective chemotherapeutic compounds. In view of the results observed by Woody and Avery, which have been confirmed in this investigation, it appears that the suggestion of Jobling and Petersen has received support in the treatment of experimental tuberculosis.

EXPERIMENTAL

Materials and Methods

Healthy guinea pigs averaging 300 to 400 gm. in weight were employed. All were inoculated with cultures of virulent human tubercle bacilli in doses of 0.4 to 4.0 mg. per kg. by subcutaneous injection in the region of the inguinal lymph nodes. In some experiments treatment was instituted three days thereafter; while in other experiments treatment was delayed for twenty-one days until tuberculous infections were well established.

Sulfone and other compounds were administered orally or by stomach tube with the expectation that each was thereby given more accurately in relation to body weight than by their incorporation in foods. Streptomycin hydrochloride in aqueous solution was administered by intramuscular injection. All animals were carefully weighed at weekly intervals. Animals dying during treatment, as well as all survivors at the termination of treatment, were subjected to careful autopsies along with histologic examinations of the inguinal lymph nodes, liver, spleen, and lungs.

The results of examination of each organ were recorded as follows:

– = no lesions
1 = occasional small tubercles or one solitary tubercle
2 = many small tubercles
3 = moderate tuberculous infection
4 = severe tuberculous infection.

By adding these numerals and dividing by the total number of guinea pigs employed, it

was found possible to express the degrees of tuberculous infection in treated and untreated animals as "the indices of infection." For example, as shown in table 3, the index for 6 animals treated with compound 150R-796 alone was 3.3; while it was 2.3 in 6 animals treated with this compound and streptomycin. The index was 8.9 in 24 untreated controls.

The toxicity of most of the compounds employed was appraised according to deaths which occurred during treatment although it is apparent that this was not a true measure of toxicity, since fatalities may have been due not only to the toxicity of the compounds administered but to tuberculous infections as well. The toxicity of all of the compounds listed in table 3 was determined in normal guinea pigs, however, along with hemoglobin estimations, total erythrocyte and leukocyte counts, and histologic examinations of the liver and kidneys of all animals for the detection of possible tissue injuries.

Compounds Employed[4]

The following compounds were employed in this investigation:

Diasone: disodium formaldehyde sulfoxylate diaminodiphenylsulfone

Promin: sodium *p,p'*-diaminodiphenylsulfone-N,N'-didextrose sulfonate

Promizole: 4,2'-diaminodiphenyl-5'-thiazolylsulfone

Sulphetrone: 4,4'-bis (γ-phenyl-N-propylamino) diphenylsulfone-tetrasodium sulfonate

150R-796: 2-(4-isothiocyanobenzenesulfonyl)-aminopyrimidine

150R-1020: 2,7-diaminothioxanthone

150R-1047: 2,7-diaminothioxanthone dioxide

150R-1079: sodium 2,7-diaminothioxanthone dioxide bis-formaldehyde sulfoxylate

150R-1130: 2,7-diaminothioxanthenol dioxide

150R-1136: sodium 2,7-diaminothioxanthenol dioxide bis-formaldehyde sulfoxylate

150R-1361: 4-amino-4'-(2-pyrimidyl) aminodiphenylsulfone

150R-1457: 3,6-diaminodibenzothiophene dioxide

150R-1560: 4,4'-diisothiocyanodiphenylsulfone

150R-1631: 4-(2-pyridylamino) 4'-nitrodiphenylsulfone

150R-1651: 4-(2-pyridylamino)-4'-aminodiphenylsulfone

150R-1777: 4-N-(2-thiazyl)-amino-4'-aminodiphenylsulfone

201R-108: N-propyl-4-*n*-tridecyl-pyridinium bromide.

RESULTS

Therapeutic effects

The results observed with 16 of the sulfone compounds administered alone in the treatment of experimental tuberculosis of guinea pigs are shown in table 1. Treatment was begun three days after inoculation. All of the compounds were

[4] Diasone, Promin, Promizole, and Sulphetrone were supplied by Parke, Davis & Company through The Wm. S. Merrell Co.; all other compounds were synthesized and supplied by The Wm. S. Merrell Co. (See J. Am. Chem. Soc., 1946, *68*, 2506; 1947, *69*, 1920, 1922, 1925.) Those compounds described as xanthenes in these articles in *J. Am. Chem. Soc.* have since (personal communication from the authors) been shown to be xanthenols.

TABLE 1

*Sulfone Compounds in the Treatment of Early Tuberculous Infection in Guinea Pigs**

COMPOUNDS	NUMBER OF ANIMALS	DOSAGE†			INDICES OF INFECTION‡
		gm/kg	Number of Doses	Total Dosage, gm/kg	
Diasone	4	0.0002	27–50	0.0054–0.010	6.5
	4	0.2	32–50	6.4–10.0	3.8
Promin	4	0.0002	50	0.010	4.5
	6	0.05	50	2.5	3.5
	6	0.1	50	5.0	3.0
	4	0.2	16–50	3.2–10.0	2.2
Promisole	4	0.0002	50	0.010	5.0
	3	0.05	50	2.5	3.7
	3	0.1	50	5.0	1.7
150R-796	3	0.005	50	0.25	6.0
	12	0.010	23–50	0.22–0.5	4.1
150R-1020	4	0.0002	30–50	0.006–0.010	7.0
150R-1047	4	0.0002	22–31	0.0044–0.0062	8.2
	3	0.005	50	0.25	7.6
	3	0.05	50	2.5	1.0
150R-1079	4	0.0002	26–50	0.0052–0.010	8.2
	3	0.005	50	0.25	7.3
	3	0.05	50	2.5	1.6
150R-1130	4	0.0002	29–50	0.0058–0.010	7.0
	2	0.005	50	0.25	4.0
	2	0.05	50	2.5	1.0
150R-1136	4	0.0002	27–42	0.0054–0.0084	9.3
	3	0.005	50	0.25	4.7
	3	0.05	50	2.5	2.6
150R-1361	4	0.0002	50	0.010	6.8
150R-1457	4	0.0002	50	0.010	5.3
150R-1560	4	0.0002	50	0.010	4.5
150R-1631	4	0.0002	27–50	0.0054–0.010	4.5
150R-1651	4	0.0002	50	0.010	3.5
150R-1777	4	0.0002	50	0.010	7.8
201R-108	3	0.0012	50	0.06	1.6
Untreated controls	10	0	0	0	8.5

* Treatment started three days after inoculation with *M. tuberculosis*.

† Twice daily by oral administration.

‡ See "Materials and Methods."

administered orally twice daily for a total of 50 doses except in those animals succumbing during the twenty-five days of treatment. The doses adminis-

TABLE 2

*Streptomycin and Sulfone Compounds Alone and in Combination in the Treatment of Early Tuberculous Infection in Guinea Pigs**

COMPOUNDS	NUMBER OF ANIMALS	STREPTOMYCIN†			SULFONE COMPOUNDS‡			INDICES OF INFECTION§
		gm/kg	Number of Doses	Total Dosage, gm/kg	gm/kg	Number of Doses	Total Dosage, gm/kg	
Streptomycin	6	0.0016	75	0.120	0	0	0	3.7
	6	0.002	75	0.150	0	0	0	3.1
Promin	3	0.002	75	0.150	0.05	50	2.5	1.7
	3	0.002	75	0.150	0.1	50	5.0	1.0
Promizole	3	0.002	75	0.150	0.05	50	2.5	2.0
	3	0.002	75	0.150	0.1	50	5.0	0.7
150R-796	3	0.0016	75	0.120	0.005	50	0.25	2.7
	3	0.0016	75	0.120	0.025	50	1.25	0.3
	3	0.002	75	0.150	0.025	50	1.25	0.7
	3	0.002	75	0.150	0.05	50	2.5	2.0
150R-1047	3	0.002	75	0.150	0.005	50	0.25	7.3
	3	0.002	75	0.150	0.05	50	2.5	2.0
150R-1079	3	0.002	75	0.150	0.005	50	0.25	3.3
	3	0.002	75	0.150	0.05	50	2.5	2.0
150R-1130	3	0.002	75	0.150	0.00005	50	0.0025	4.0
	3	0.002	75	0.150	0.0005	50	0.025	5.7
	3	0.002	75	0.150	0.005	50	0.25	4.7
	2	0.002	75	0.150	0.05	50	2.5	5.0
150R-1136	3	0.002	75	0.150	0.005	50	0.25	3.7
	3	0.002	75	0.150	0.05	50	2.5	0.67
Untreated controls	12	0	0	0	0	0	0	9.8

* Treatment started three days after inoculation with *M. tuberculosis*.
† By intramuscular injection every eight hours.
‡ By oral administration twice daily.
§ See "Materials and Methods."

tered per kilogram of weight are shown in the table as are the total amounts of each compound administered.

It will be observed that the infection index of 10 untreated control animals was 8.5. From the standpoint of the largest doses administered, the best therapeutic results or lowest infection indices were observed with 150R-1047 and

150R-1130, followed in order of effectiveness by 150R-1079, 201R-108, Promizole, Promin, 150R-1136, 150R-1651, Diasone, 150R-796, 150R-1560, 150R-1631, and 150R-1457. Compounds 150R-1020, 150R-1361, and 150R-1777 were less effective.

Seven of these compounds were then administered orally twice daily for 50 doses along with intramuscular injections of streptomycin hydrochloride every eight hours for a total of 75 injections over a period of twenty-five days. Treatment was begun three days after inoculation. The results are summarized in table 2 which also shows the dose of each compound per kilogram of weight and the total amounts administered.

In this experiment the infection index of 12 untreated control animals was 9.8 and that of 12 animals treated with streptomycin alone, 3.1 to 3.7. From the standpoint of the largest doses administered, it will be observed that all of the compounds showed some degree of synergistic or additive activity with streptomycin. The lowest infection indices were observed with 150R-1136 (0.67), Promizole (0.7), and Promin (1.0), followed in order by 150R-796 (2.0), 150R-1047 (2.0), 150R-1079 (2.0), and 150R-1130 (5.0).

In the third experiment, treatment was not begun until twenty-one days after inoculation, when tuberculous infections were well established. Seven compounds, including Promin, Promizole, Sulphetrone, and potassium iodide, were administered alone and in combination with streptomycin. All of the compounds were administered orally twice daily. In combined treatment, streptomycin hydrochloride by intramuscular injection was also administered twice daily at the same time. Treatment was given over a period of twenty days (40 doses) except in the case of some animals that died during the period of treatment. The results are summarized in table 3 which also shows the doses of each compound per kilogram of weight and the total amounts administered.

In this experiment the infection index of 24 untreated control animals was 8.9 and that of those treated with streptomycin alone, 2.7. It will be observed that potassium iodide alone gave an infection index of 6.3 and an index of 2.1 when administered along with streptomycin, a finding indicative of synergistic or additive activity. Since 80 mg. per kg. were given twice daily (double the dose administered by Woody and Avery), the total dose was too high and some animals succumbed during the period of treatment apparently because of toxic effects. The infection indices of the remaining 6 sulfone compounds administered alone, including Sulphetrone, varied from 3.3 to 3.8 while the infection indices of the compounds administered along with streptomycin varied from 2.0 to 2.7.

Results of Toxicity Studies

Toxicity studies employing normal guinea pigs were conducted with all of the compounds listed in table 3 except potassium iodide and streptomycin. Promin, 150R-796, 150R-1079, and 150R-1136 were given in doses of 0.025, 0.05, 0.1, and 0.2 gm. per kg. twice daily for 40 doses in succession. All animals survived, indicating that total doses as high as 8 gm. per kg. of these compounds were well borne. Owing to a limited supply of Sulphetrone, only 0.025 and 0.5

gm. per kg. twice daily for 40 doses were administered, and all animals survived. Promizole was given in doses of 0.1, 0.2, 0.3, and 0.4 gm. per kg. twice daily. All animals given 40 doses survived, the total dosage reaching as high as 16 gm. per kg.

TABLE 3

*Streptomycin, Potassium Iodide, and Sulfone Compounds Alone and in Combination in the Treatment of Established Tuberculous Infection in Guinea Pigs**

COMPOUNDS	NUMBER OF ANIMALS	STREPTOMYCIN†			OTHER COMPOUNDS‡			INDICES OF INFECTION§
		gm/kg	Number of Doses	Total Dosage, gm/kg	gm/kg	Number of Doses	Total Dosage, gm/kg	
Streptomycin	6	0.003	40	0.120	0	0	0	2.7
Iodide	6	0	0	0	0.08	10–40	0.8–3.2	6.3
	6	0.003	40	0.120	0.08	32–40	2.56–3.2	2.1
Promin	6	0	0	0	0.05	40	2.0	3.5
	6	0.003	40	0.120	0.05	40	2.0	2.0
Promizole	6	0	0	0	0.1	40	4.0	3.7
	6	0.003	40	0.120	0.1	40	4.0	2.3
Sulphetrone	6	0	0	0	0.05	40	2.0	3.7
	6	0.003	40	0.120	0.05	40	2.0	2.5
150R-796	6	0	0	0	0.025	40	1.0	3.3
	6	0.003	40	0.120	0.025	40	1.0	2.3
150R-1079	6	0	0	0	0.05	40	2.0	3.8
	6	0.003	40	0.120	0.05	40	2.0	2.7
150R-1136	6	0	0	0	0.05	40	2.0	3.7
	6	0.003	40	0.120	0.05	40	2.0	2.3
Untreated controls	24	0	0	0	0	0	0	8.9

* Treatment started twenty-one days after inoculation with *M. tuberculosis*.
† Twice daily by intramuscular injection.
‡ Twice daily by oral administration.
§ See "Materials and Methods."

Two preliminary hemoglobin estimations, total erythrocyte and total leukocyte counts, of all animals were made before the administration of the compounds. These blood examinations were repeated twice weekly over the period of twenty days of treatment. Promin produced hemolytic anemia in all animals, especially those given 0.05, 0.1, and 0.2 gm. per kg. twice daily for 40 doses. Promizole, Sulphetrone, 150R-796, and 150R-1136 also produced mild degrees of hemolytic anemia, especially in the larger doses. No evidences of anemia were detected in the animals given 150R-1079.

None of the compounds produced changes in the total leukocyte counts except Promin and 150R-796. Promin showed a tendency to produce leukocytosis, while 150R-796 apparently depressed the bone marrow with the production of a mild degree of leukopenia. Promizole has also been found to produce leukopenia in some cases of human tuberculosis, but this change was not observed in the normal guinea pigs of the present study.

As previously stated, all animals were autopsied. There were no detectable gross evidences of toxicity in the kidneys, suprarenal glands, liver, spleen, heart, or lungs. Histologic examinations of the kidneys and livers of all animals showed no evidences of injury except, possibly, slight degrees of congestion in a few animals. Examinations of the thyroid glands were not made.

SUMMARY

1. A method is described for appraising the therapeutic activity of compounds employed in the treatment of experimental tuberculosis on the basis of determination of the "infection index."

2. By the use of this method the therapeutic effects of streptomycin, Diasone, Fromin, Promizole, Sulphetrone, potassium iodide, and thirteen new sulfone compounds were determined in the treatment of experimental tuberculosis of guinea pigs. With the exception of three of the new sulfone compounds, all showed definite degrees of therapeutic activity.

3. The therapeutic effects of Promin, Promizole, Sulphetrone, potassium iodide, and five of the new sulfone compounds administered along with streptomycin were also determined; all showed evidences of synergistic or additive chemotherapeutic activity of varying degrees. In view of these synergistic or additive chemotherapeutic effects, it appears that combination chemotherapy of human tuberculosis with streptomycin and sulfone compounds is worthy of clinical trial.

4. The toxicity of Promin, Promizole, Sulphetrone, and three of the new compounds for normal guinea pigs was determined. Promin, Promizole, Sulphetrone, and two of the new sulfone compounds produced varying degrees of hemolytic anemia, especially Promin. Leukocytic changes were also produced by Promin and one of the new sulfone compounds. None of these six sulfone compounds, however, produced gross or histologic changes in the kidneys, suprarenal glands, liver, spleen, heart, or lungs ascribable to tissue injury; examinations of the thyroid glands were not made.

SUMARIO

Los Compuestos Sulfónicos y el Yoduro Potásico Solos y Combinados con la Estreptomicina en el Tratamiento de la Tuberculosis Experimental del Cobayo

1. El método descrito permite justipreciar la actividad terapéutica de los compuestos empleados en el tratamiento de la tuberculosis experimental a base de la determinación del "índice de infección."

2. Determináronse los efectos terapéuticos de la estreptomicina, la Diasona, la Promina, el Promizol, la Sulfetrona, el yoduro de potasio y trece nuevos compuestos de la sulfona en el tratamiento de la tuberculosis experimental de los cobayos. Exceptuados tres de los nuevos compuestos sulfónicos, todos revelaron grados bien definidos de actividad terapéutica.

3. También se determinaron los efectos terapéuticos de la Promina, el Promizol, la Sulfetrona, el yoduro de potasio y cinco de los nuevos compuestos sulfónicos al ser administrados junto con la estreptomicina, revelando todos en mayor o menor grado signos de actividad quimioterapéutica sinérgica o aditiva. A la luz de esos efectos quimioterapéuticos sinérgicos o aditivos, parece que vale la pena ensayar clínicamente la terapéutica combinada de la tuberculosis humana con estreptomicina y compuestos de la sulfona.

4. Se determinó la toxicidad de la Promina, el Promizol, la Sulfetrona y tres de los nuevos compuestos para los cobayos normales. La Promina, el Promizol, la Sulfetrona y dos de los nuevos compuestos sulfónicos, y sobre todo la Promina, produjeron en mayor o menor grado anemia hemolítica. También produjeron alteraciones leucocitarias la Promina y uno de los nuevos compuestos sulfónicos. Sin embargo, ninguno de los seis compuestos de la sulfona provocó alteraciones macroscópicas o histológicas en los riñones, suprarrenales, hígado, bazo, corazón o pulmones que fueran imputables a lesión histológica. No se ejecutaron exámenes de los tiroides.

RESUME

Composé sulfonés et iodure de potassium soit séparément soit en combinaison avec la streptomycine dans le traitement de la tuberculose expérimentale chez le cobaye

1. Une méthode permettant d'évaluer l'activité thérapeutique de composés utilisés dans le traitement de la tuberculose expérimentale sur la base de détermination de "l' indice d'infection" est décrite.

2. Les effets thérapeutiques de la streptomycine, du Diazone, du Promin, du Promizole, du Sulphetrone, de l'iodure de potassium et de 13 nouveaux composés sulfonés ont été évalués dans le traitement de la tuberculose expérimentale du cobaye. A l'exception de trois des nouveaux composés sulfonés, à des degrés divers, tous faisaient preuve d'une activité thérapeutique définie.

3. Les effets thérapeutiques du Promin, du Promizole, du Sulphetrone, de l'iodure de potassium et de 5 des nouveaux composés sulfonés administrés en même temps que la streptomycine ont été également déterminés; tous ont fait preuve, à des degrés variés, d'une activité chimiothérapique synergique ou additive. En raison de ces effets chimiothérapiques synergiques ou additifs il apparaît que la chimiothérapie combinée de la tuberculose humaine par l'association de la streptomycine et des composés sulfonés en justifie l'essai clinique.

4. La toxicité du Promin, du Promizole, du Sulphetrone, et de 3 des nouveaux composés a été déterminée chez le cobaye. Le Promin, le Promizole, le Sulphetrone et deux des nouveaux composés sulfonés ont déterminé une anémie hémo-

lytique de degrés variés. Des modifications leucocytaires ont été également produites par la Promin et par un des nouveaux composés sulfonés. Toutefois aucun de ces 6 composés sulfonés n'a déterminé d'altération microscopique ou macroscopique dans le rein, la surrénale, le foie, la rate, le coeur ou les poumons pouvant être attribuées à une lésion du parenchyme; la glande thyroïde n'a pas été examinée.

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Editorial

The Creative Spirit in Research

Current approaches to research, made familiar by the coordinated efforts of the war period, look complicated when compared to Benjamin Franklin's accomplishment with a kite, a silk thread, and a key. It has become the fashion to conduct large-scale cooperative research programs for ferreting out fact, compiling and comparing data, and evaluating regimens of clinical procedure, notably true of work on new therapeutic agents. This type of effort has enabled us to know promptly what a given product or procedure will do to man's disease and man's body and has led to acquisition of valuable practical fact. Cooperative efforts have laid down in record time an array of knowledge of the advantages and disadvantages of several drugs which would have required years for accumulation by conventional means and have thus set rational therapy ahead. As a consequence, patients are treated more rationally than otherwise could have been possible in the time elapsed since the new chemotherapeutic era began.

In respect to tuberculosis, this type of research has been highlighted particularly by recent efforts of both official and voluntary agencies and has involved the labor of many hundreds of people. Never in the history of medicine has such an undertaking been launched upon such a scale and never have more useful results come from such efforts.

This type of study is valuable and it merits continued support. Yet it possesses certain limitations, even dangers, to the progress of investigative medicine which, unless we are continually aware of them, may blind us to the need of other approaches. Coordinated efforts tend to stress compilation and comparison but are sometimes relatively sterile of new ideas and often fail to stimulate *new* discoveries. Recognized for what it is, this type of investigation is splendid, but it should not be thought of as the embodiment or the beginning and end of research.

We should recognize two types of research, namely: the ascertaining of fact by requisite techniques; and the operation of the creative desire. The former, many can do; the latter can be done only by a few. Investigators in the latter category need time simply to think, time to rationalize their thinking, and time to put their thoughts to the test. Koch formulated his four laws long before he applied them to the discovery of the tubercle bacillus. Geniuses like Pasteur, Bernard, Edison, and Einstein were philosophers, thinkers, and even artists or mystics before they were doers. There is something about the creative spirit that must be individual, independent, something that seems to defy regimentation or the "command performance." It is born of imagination, interest, curiosity, and questioning; it is the factor which causes one to ask eternally "why" or "how" and is the factor which maintains an attitude of inquiry. A person

possessed of such a creative spirit may produce research of varying quality both in theory and in application. From him some inane ideas will come, but some of his creative acts will also be of the greatest service to man. His experience, often mystical in nature, is sometimes of world-moving significance. It is something precious that should be cherished. It seeks truth still under the ancient teaching that: "Ye shall know the truth and the truth shall make you free."

Research dominates much of our thinking these days, whether it be in literature, history, religion, science, or medicine. It is usually as good as the ideas that go into it. It may be a highly sophisticated exercise that drives people forward into seeing new relationships. It may be carried out individually or by groups; it may be simple or complicated, practical or theoretical. No matter the type of study, no matter whether individuals or groups are concerned, no matter the nature of the issue at hand, I repeat that imagination, interest, curiosity, and everlasting questioning compose the fountain head.

Someone has written that science is a "sacred cow." It can at least be said that the scientist has a sacred trust which should be nourished and cherished for the quests that are made in the name of science. Our services must support the individual with a creative interest whether he is in a small unit or a large one and whether he carries on in solitary or group fashion. And the support should consist not of facilities only, but of time, leisure, and an environment conducive to quiet reflection as well as active work. When Laennec pointed to the unity of phthisis, Villemin to the infectiousness of the disease, Koch to the actual causative agent, and Pirquet to the vast difference between tuberculous infection and tuberculous disease, they each represented research of the highest order and were the parents to a rich harvest of new knowledge. It is the same with the basic elements of therapy. Bed rest, collapse therapy, and chemotherapy need no advocate, but how much patient, painstaking study and work were expended in each of these fields to bring them into modern realization!

The connections and chain relationships of research have been stated recently in great clearness and brevity by Long as follows:

> It must not be forgotten. . . . that each major discovery in medicine has resulted only through the summation of a vast number of major and minor discoveries in the same and quite different fields. The tubercle bacillus would not have been discovered without the microscope and the microscope could not have been invented and improved without exhaustive physical and mathematical investigation of refracting lenses. X-ray photography would be impossible without suitable light-sensitive materials, which did not become available purely by accident. Modern laboratory and clinical diagnosis of tuberculosis, its sanatorium, surgical and chemotherapeutic treatment, and the facts of epidemiology and public health, all have resulted from a synthesis of a huge amount of research. Chance entered into many important observations, but exact investigation has always been the next step after a lucky accidental find (Am. Rev. Tuberc., 1949, *60*, 527).

Some have questioned, however, whether we need continuation of research in tuberculosis which has dropped far from its long-established place of pre-emi-

nence in the list of the causes of death. Death rates are declining steadily, and some people are talking now as though the issue has reached a distinctly minor level. Possibly we have paid too little attention to tuberculosis as a cause of prolonged invalidism, of wrecked families, of economic loss, and, perish the thought, have given too much attention to the death rate, even though for the young and the active it is still the first cause; from elderly men, it still requires a heavy tribute; for certain races, it is still a stark reality. Edwards and Drolet (Am. Rev. Tuberc., 1950, *61*, 39) have suggested that we "raise our sites from the cemeteries . . . to the living tuberculous. . . ." As long as tuberculosis produces loss, suffering, misery, and death, it rates attack from every point of view. Much is known about its nature and habits, its mode of spread, and its characteristics as it develops in the body; and much, too, about its treatment. But much more is not known and many patients still suffer and die from the want of knowledge.

Do we need more research? Answer to this question may come from a brief look at what may be called our "areas of ignorance." Among many other items one may point to our lack of understanding of the relationships between primary and reinfection, or ask what causes conversion of mere infection into clinical disease. Why do miliary tuberculosis and tuberculous meningitis occur more commonly in the younger ages? How do our biochemical studies fare? What about our sketchy knowledge of immunity, and what ought to be done about BCG? What do we know of sociologic problems, economic and statistical approaches that relate to chronic illness, and is it not true also that we actually know very little about racial reactions to the disease? The entire subject of "air sanitation" is begging for an answer. Even tuberculin therapy is being reworked. Some have joined its use with that of streptomycin in the treatment of tuberculous meningitis. It is known that tuberculin produces increased specific inflammation in and around foci of tuberculosis and facilitates absorption and spread of bacilli. Use of these substances in combination may serve to "flush" the bacilli by tuberculin and "shoot" them by streptomycin as they scurry for a new home. Such studies are fraught with danger but also, if carried out intelligently and with full knowledge of the potentialities, may lead to desirable results.

Areas of ignorance are being surveyed. It is a thrilling experience to sit in on a meeting of the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association, and to see what diversity of research effort is being supported. The roll call is an imposing one, covering numerous studies of clinical, chemical, biologic, bacteriologic, and immunologic types.

Who should do research? The man at the bedside confronted with serious problems in diagnosis or therapy needs more of the products of research, but many who have daily contact with the needs of sick people are impatient with any efforts beyond the very practical. Ideally each of these physicians needs an absorbing interest in the unexplained phenomena before him, and, ideally,

the question "why" should return so often to him as to force efforts at satisfying his curiosity. All of us become research workers in proportion to the intensity of our interest, the range of our ingenuity, and the depth of our understanding, imagination, and wisdom. May it not properly be said that research is a state of mind—an attitude of life—a questioning of the "hows" and "whys" of the unknown about us? If so, many can be researchers in spirit and in truth.

STUART WILLIS

Correspondence

DIAGNOSTIC STANDARDS—1950 EDITION

To the Editors of the American Review of Tuberculosis:

I enclose a letter to Dr. David Salkin in reference to his letter on *Diagnostic Standards* published in the June issue of the REVIEW.

Sincerely yours,
JOHN D. STEELE

May 9, 1951

Dr. David Salkin
Chief, Professional Services
Veterans Administration Hospital
San Fernando, California
Dear Dr. Salkin:

Your recent letter to the Editors of THE AMERICAN REVIEW OF TUBERCULOSIS in regard to the clinical classification of the 1950 edition of DIAGNOSTIC STANDARDS, which was published in the June 1951 number of the REVIEW, has been referred to me for reply since I was chairman of the subcommittee responsible for this classification.

In general, I agree personally with your comments. The points you raise were considered at length by the Committee. I will try to explain why the clinical classification was published in its present form and not in the form which you and I and others might have preferred.

As you know, ideas on the therapy of pulmonary tuberculosis vary widely in different parts of this country; concepts as to the results of therapy vary just as widely. Thus, any classification primarily concerned with the results of therapy must be broad enough to cover these variations and must necessarily represent a compromise between conflicting views.

Although there is a carefully worded introduction to the 1950 edition of DIAGNOSTIC STANDARDS, I am afraid that many users of this volume are inclined to turn immediately to other sections without reading it. Let me quote a few excerpts from this introduction. ". . . experience . . . has demonstrated unequivocally that complete agreement with respect to the (clinical) classification, even among the most experienced clinicians in the country, is impossible. The classification presented . . . represents a well-considered compromise. . . ." "It is not to be expected that the classification will meet universal approval, since a considerable amount of individualism prevails in clinical concepts in this field." "(DIAGNOSTIC STANDARDS) is a general guide to be used with such modifications in practice as seem essential. It should serve to promote common understanding and prevent the confusion and misunderstanding in terms and concepts that would prevail if there were no such document."

As to your comments in regard to adequate roentgenologic examinations, I believe this is covered in the section on roentgenologic diagnosis (page 55). A few excerpts from this section follow. "It is impossible to show on one film all conditions present in the lungs." ". . . additional roentgenograms must be made with the patient in different positions. Those most commonly used are the anterio-posterior, the lordotic . . . the lateral . . . the oblique stereoscopic views." ". . . planigraphy also has its place."

As to your comment in regard to the term "arrested," this category represented the greatest stumbling block our committee had to face. Personally I would have preferred to call this group "apparently inactive" and to limit it to those patients whose pulmonary secretions are negative on concentrate and have not been cultured because of lack of facilities. However, I was merely one member of the Committee and, if we had not reached a compromise on this point, we would still be using the 1940 classification. Nevertheless, the 1950 classification is sufficiently flexible so that those who feel as we do can easily disregard this category and classify their "arrested" patients as "active" if they care to do so. You will probably be interested to know that the new forms used by the Wisconsin State Board of Health make no provision for "arrested" (they are either "active" or "inactive").

As to your comment in regard to the exercise status, you will note that the exercise classification as adopted was based on the old exercise requirements. This was done intentionally so that there would be less confusion in transposing the old terms into the new terms (page 40). I quite agree that this part of the classification might have been simplified, but there seemed to be a definite advantage in being able to transpose the new and old terms fairly accurately.

In the proposed classification which you and Dr. Cadden published in 1941, which included active and inactive categories, you did not actually propose a separate exercise classification. You stated that exercise was to be omitted entirely. There was considerable discussion on this point by our Committee. The proponents of exercise as an integral part of the classification finally won. At least with the new separate exercise classification, amputees and respiratory cripples who cannot take "one hour's walking exercise daily, or its equivalent" now can be classified more logically than under the old classification.

The committee has received very few comments on the new classification. We hope that this silence denotes approval. Perhaps many believe, as you and I do, that the new classification is a "step in the right direction" and are hoping for perfection in the next edition.

Sincerely,

May 7, 1951 JOHN D. STEELE

Books

PLAN FOR CONTROL PROGRAMMES, SUGGESTIONS FOR THE CONTROL OF TUBERCULOSIS IN COUNTRIES WITH UNDEVELOPED AND UNDERDEVELOPED PROGRAMMES, World Health Organization Technical Report Series No. 7, Palais des Nations, Geneva, Switzerland, April 1950.

In some countries of the world, the facilities and organizations ordinarily responsible for tuberculosis control measures are nonexistent or nearly so, and some may be inclined to accept such situations as hopeless. Fortunately, there are others with more optimistic and aggressive attitudes.

At its Fifth Session in September 1950, the World Health Organization Expert Committee on Tuberculosis asked that attention be called to Annex 1 of the Report on the Fourth Session.

This document is a straightforward exposition of practical steps to take when improvements in such basic things as nutrition, housing, education, and the general standard of living are likely to be delayed. Three main objectives are stated:

(1) the prevention of spread of tuberculosis from known infectious cases
(2) the protection of groups highly exposed to tuberculosis and most likely to get the disease
(3) the furthering of all other preventive and curative measures, including after-care and rehabilitation.

A summary of the steps, in the order they might be taken, is as follows:

1. *Survey of the Needs, Resources, and Attitudes of the People.* This should be done by an expert (from the outside, through WHO if necessary) and might include sampling of various segments of the population by tuberculin tests and mass radiography. Information would be obtained from official and voluntary groups and individuals most concerned with the problem. Speed is important.
2. *Recruitment and Training of Personnel.* A leader and a central group must be found, or trained, to cover the activities of public health administration, epidemiology, laboratory and clinical work, and public health nursing. The leader must be a government employee and the official to be in charge of tuberculosis control.
3. *Exact Diagnosis.* It is essential to have laboratory service available for the demonstration of tubercle bacilli by modern culture methods.
4. *Records.* Even the most rudimentary system should indicate which cases definitely have been diagnosed by laboratory examination. Eventually, reporting should be compulsory.
5. *Home Nursing Service.* Where the ideal of hospital isolation of patients is impossible, visiting nurses can teach patients and families proper ways to dispose of infectious material and how to obtain at least partial isolation of the patient at home.
6. *Dispensaries.* These should be centers for tuberculosis control and, if possible, associated with existing hospitals or public health centers. They should emphasize the preventive and social aspects, including examination and care of contacts, supervision and after-care of patients, and home visiting.
7. *Hospital Facilities.* A realistic plan should be developed. The principal purpose is to provide isolation of infectious cases. Adequate personnel and equipment are essential, but the buildings may be of simple, inexpensive construction and should be near centers of population. Adequate aftercare is important.

8. *Other Measures.* BCG vaccination will be effective only as a part of a general control program.

Throughout the development of the control program there should be intensive education of the public in the importance of tuberculosis, and the plan for control. This can be facilitated by cooperating national and local voluntary organizations. This assumes that voluntary groups are in existence. The desirability of organising a voluntary tuberculosis association as one of the first steps should be emphasized. Mass radiography should not be employed until there are facilities for exact diagnosis and supervision of patients. If it is known there are large numbers of expectorating persons, sputum examinations of this group will be less costly than mass radiography in identifying the principal sources of spread.

Although the plan outline in this WHO report was prepared for less fortunate parts of the world, the steps recommended are applicable to areas of the United States where facilities are still inadequate.

FLOYD M. FELDMANN

DIAGNOSTIC STANDARDS AND CLASSIFICATIONS OF TUBERCULOSIS, 1950 Edition, National Tuberculosis Association, New York, 1951, Price, $0.25.

The introduction to this revision of *Diagnostic Standards* states that it is the "ninth one incorporating fundamental new material or significant departures from previous texts." A careful reading of the entire manual reveals that much that is new has indeed been added. Current concepts of pathogenesis and their relation to the diagnosis and clinical course of tuberculosis are well stated in the sections devoted to these subjects. The importance of mass roentgenographic surveys and of vocational rehabilitation in modern practice are recognised by new sections which outline their respective methodologies. The chapter on technical procedures brings up to date the techniques of tuberculin testing and of demonstration of the tubercle bacillus. It presents as well a carefully considered definition of the "negative" sputum.

In addition to discussion of the technical factors involved in obtaining roentgenograms of the chest, this section presents very ably the aims and limitations of roentgenology as well as pertinent remarks on the interpretation of chest roentgenograms.

Probably all of these sections represent compromises as they touch upon controversial matters, and their authors will continue to be critical of their present form. This must be particularly true of the section containing the new clinical classification. It is apparent that the aim here is to achieve simplicity by an inclusive classification of only two categories, *active* and *inactive*. It is also apparent that the third category of *arrested* represents a compromise to include those otherwise inactive patients whose sputum or gastric washings may be occasionally positive for tubercle bacilli by sputum concentration, culture, or animal inoculation; or those whose sputum concentrates are negative, but for whom more intensive studies are not available.

Anything that can be said in criticism of this classification certainly has been said repeatedly by its authors during the two years of its development. In its favor is its comprehensive and generally permissive nature. For example, it is entirely possible, where facilities for intensive bacteriologic study are available, to drop the category of *arrested* and classify patients as either *active* or *inactive*. This has already been done effectively by at least one state board of health.

To aid in the adoption of an entirely new classification, a useful table of comparison of the 1940 and 1950 terminology has been added.

Another new and valuable addition is the outline of Jackson and Huber's terminology of bronchopulmonary segments, well illustrated from the diagrams in Gray's *Anatomy*.

The implications of the new classification and the limitations of classifications in general have been clearly stated in the introduction, which should be read.

Indeed, the excellent integration of the various sections requires that this edition of *Diagnostic Standards* be read in its entirety.

The responsible committees are to be congratulated on the successful completion of a difficult and tremendously important task.

GEORGE C. OWEN

YOU'RE HUMAN, TOO! By Adele Streeseman. Pp. 206, Coward-McCann, Inc., New York, 1950, Price, $3.00

Book reviewers are human too, especially those for whom no deadline has been set by a stern editor. The book to be reviewed may be perused immediately on arrival and mental notes made, but many weeks may elapse before these notes reach paper.

Such was the case with Doctor Streeseman's book which traveled from my office shelf to a patient's library and back again before this review was written. Indeed, this book, unlike many other popularizations of psychiatric material, has an important function to perform in passing from the hands of the physician to the layman. Doctor Streeseman, whose vast experience as industrial physician and medical advisor to the Women's Prison Association of New York City has brought her into contact with many people in trouble, uses current analytic and psychodynamic concepts to interpret human problems, such as gambling, alcoholism, homosexuality, and suicide, in a warm sympathetic manner.

The material in this book is not new—some issues are oversimplified—and the claims made for psychoanalysis as a therapeutic tool will appear exaggerated to many physicians. Nevertheless, this is a useful and important book for the physician to put in the hands of his patient because it is not just another piece of nihilism but suggests, to quote William Faulkner, "that man may prevail."

BEATRICE BERLE

I TOOK IT LYING DOWN. By Marian Spitzer. Pp. 247, Random House, Inc., New York, 1951, Price, $2.75.

I Took It Lying Down by Marian Spitzer is an intensely interesting autobiographical account of the adjustments and maladjustments of a vital personality to the acceptance of having pulmonary tuberculosis. It is unique in this phase of literature because the author is not only well trained in writing but is astonishingly honest and analytical in her objective approach to her own conscious and subconscious mind. And fortunately for the recital, she displays a keen though restrained sense of humor.

I Took It Lying Down will prove to be an excellent textbook for patients with this disease. Her reaction to the dreaded diagnosis, the adjustment to the isolation and to rest treatment, her conquest of monotony, her gradual acquiescence in the routine of living, and the development of a state of passive waiting are all lessons and moods that the patient reader has himself experienced.

There are lessons here for the patient still under active treatment and for those who have recently returned to a "normal" but, if he is wise, a restricted life. He can profit by Miss Spitzer's unfortunate mistakes of routine which led to relapses. I am sure that this

book will also prove to be profitable, especially for the family with a member who is taking sanatorium treatment.

One of the pleasures of a reader who specializes in the treatment of tuberculous patients is to note the wise way in which her doctors handled the supervision of this difficult patient. The dynamic, creative individual has impulses which make more difficult the development of the virtues of patience and equanimity. Living with tuberculosis is a way of life. This is an account of Miss Spitzer's way—and of her final victory.

J. N. HAYES

PULMONARY VENTILATION AND ITS PHYSIOLOGICAL REGULATION. By John S. Gray. Pp. xii–82, Charles C Thomas, Springfield, Ill., 1950, Price, $2.00.

This small monograph is essentially a product of Doctor Gray's research at Randolph Field in World War II. Using extensively the data from respiratory studies published previously, he defined more clearly than previous workers the relationships that exist among the interdependent factors which regulate the ventilation of the lungs. A clear argument is made that the pulmonary ventilation at any time is determined by the algebraic sum of several partial effects, the magnitude and direction of the influence being specific for each factor. Thus, an increase in alveolar and arterial partial pressure of CO_2 tends to augment breathing, whereas a reduction of this value tends to inhibit breathing. In hyperpnea due to hypoxemia, the low partial pressure of O_2 is a powerful stimulus but the net increase in ventilation is slight because, metabolism not being significantly elevated, the tendency to hyperventilate reduces the CO_2 level and decreases hydrogen ion concentration. Both of the latter effects have a marked inhibitory action on lung ventilation. Factors other than chemical, such as the numerous respiratory reflexes, must of course be included in the integration of respiratory activities.

The presentation of the concept is well done. There are enough allusions to clinical problems to make the volume of interest to clinicians as well as to physiologists. Specific examples are the discussions of metabolic acidosis, CO_2 adaptation in emphysema, and the case against CO_2 administration in resuscitation emergencies. However, little attention is paid to the influence of factors commonly encountered clinically, such as the influences of increased resistance to air flow in the conducting passages, parenchymal exudates and transudates, and pulmonary vascular disease.

In the opinion of this reviewer, the author has made an important contribution to our understanding of the chemical control of breathing. He may have oversimplified the problem, and it is questionable whether anything is to be gained by designation of his concepts as the Multiple Factor Theory. The format of the book is excellent.

JAMES L. WHITTENBERGER

LES MALADIES DES BRONCHES—ÉTUDE ANATOMIQUE PHYSIOPATHOLOGIQUE, CLINIQUE ET THÉRAPEUTIQUE. By Jacques Lecoeur. Pp. 608 with 240 illustrations, Vigot Frères, Editeurs, 25 Rue de l'Ecole de Médecine, Paris, 1950.

This excellent edition of a classical textbook for the French chest physician illustrates the many medical advances made since the days of Laennec when bronchitis and dilatation of the bronchi constituted the total knowledge of diseases of the bronchi. The book is richly illustrated with reproductions of microscopic slides, resected specimens, roentgenograms, and a few tables. They are well chosen and, for the most part, technically

excellent. However, the roentgenographic illustrations, like those of so many European works, are printed in the negative rather than in the positive print. The material in the text is presented in eleven chapters.

Chapter 1 deals with the anatomy, physiology, and pathology of the bronchial apparatus.

Methods of endobronchial exploration, bronchoscopy, and bronchography are fully described in Chapter 2. It is of interest that bronchoscopic lens systems permitting right angle and retrograde vision have recently been made available by French manufacturers.

In Chapter 3, acute and chronic bronchitis is discussed in great detail.

Chapter 4 deals with clinical syndromes due to obstruction of the large bronchi. The importance of bronchopulmonary segments in conditions of emphysema and atelectasis is stressed.

Bronchogenic tumors are discussed in Chapter 5. In the absence of confirmatory diagnostic criteria, exploratory thoracotomy is recommended as being as simple and inoffensive a procedure as an exploratory laparotomy. The racial distribution of bronchogenic carcinoma is presented as a varied pattern with predominance in the Hebrew and a rarity in the Negro. There are no valid statistics presented to back these assumptions. The author states that he finds it difficult and premature to accept tobacco smoking as an etiologic factor in bronchogenic carcinoma.

Chapter 6 deals with tumors such as fibroma, lipoma, papilloma, leiomyoma, chondroma, osteoma, and angioma. Extrinsic compression of the bronchi by mediastinal tumors, pulmonary tumors, and enlarged hilar nodes are discussed in the latter half of the chapter.

Endobronchial tuberculosis is covered in forty-nine pages of Chapter 8. It is reported as being more common in people less than thirty-five years old, with females predominating three to one. It is regrettable that the greatest advance in specific treatment, streptomycin, is dismissed in one sentence: "Finally, we cannot end this brief introduction without mentioning the therapeutic role of streptomycin which has favorably modified the evolution and prognosis of these lesions." This brevity is in marked contrast with the two pages in Chapter 3 devoted to the listing of therapeutic agents in the treatment of nontuberculous bronchitis. On the other hand, it serves to emphasize that, where we have many therapeutic agents for a condition, in reality we lack an effective one.

Chapter 9 is the shortest chapter in the book, and contains nine pages devoted to nontuberculous superficial lesions of the bronchial mucous membranes and to broncholithiasis.

Degenerative lesions of the bronchi are covered in Chapter 10 which deals with bronchiectasis. Credit is given the American statistics for influencing surgical intervention in bronchiectasis by employing wedge resection, lobectomy, or pneumonectomy.

Chapter 11, the final chapter, deals with bronchogenic cysts.

The material presented in this textbook lends itself to quick reading and easy retention inasmuch as the outline form is frequently used with the significant points enumerated.

The paper is of high quality. The type is predominantly old style roman with free use of modern italic print.

Coincident with the recent increased interest in diseases of the chest, this book serves to implant the proper importance of the bronchial tree as related to respiratory pathology. It is correctly labeled as an anatomic, physiologic, pathologic, clinical, and therapeutic compilation. As a result of a visit to the United States, the author is rather familiar with American reports. Unfortunately, although he quotes freely from the American literature, he fails to include a bibliography which would have served as an excellent compilation

of American and European thinking in regard to the bronchial tree. Otherwise, the book leaves little to be desired.

EDWARD DUNNER

A SYLLABUS OF LABORATORY EXAMINATIONS IN CLINICAL DIAGNOSIS. Edited by Thomas Hale Ham. Pp. 496 with illustrations, Harvard University Press, 1950, Cambridge, Massachusetts, Price, $5.00.

This volume was developed as a part of the second-year course in Laboratory Diagnosis at Harvard Medical School and is designed primarily for the physician and student in clinical medicine. The orientation of the text is that a "laboratory procedure begins and ends with the patient." The book is composed of twenty-seven units which are distributed into seven categories related to laboratory examinations of the various body systems and their diseases.

The first three units are devoted to a general introduction to laboratory examinations. Thirteen excellent units concern laboratory examinations of the blood. Two units are devoted to each of the following topics: laboratory examination related to the urinary system, special tests related to infectious diseases, and special tests related to the diseases of metabolism. Four units comprise the section on laboratory tests related to disease of the gastrointestinal tract and one unit is given to the special tests related to extravascular fluids.

Each unit describes laboratory examinations from the standpoint of clinical value, availability, principal method, and the limitations and interpretations of each particular test. The interpretations are specifically oriented to the use of test as a diagnostic aid in relation to the history and physical examination of the patient. In addition, a most interesting section on the current cost of laboratory examinations and certain laboratory apparatus is presented.

The editor of this volume is to be congratulated, as are the thirty-two contributors for having made such a concise yet comprehensive presentation of the data. The practicing physician, the teacher, and the student of medicine will find that this book fulfills its aim as a most valuable contribution to the use and understanding of laboratory examinations in clinical medicine.

CHARLES A. LE MAISTRE

BOOKS RECEIVED

PERSONNEL ADMINISTRATION IN PUBLIC HEALTH NURSING. By William Brody. Pp. 209, C. V. Mosby Company, St. Louis, 1951, Price, $3.25.

HEALTH OF FERROUS FOUNDRYMEN IN ILLINOIS. Pp. 130, Public Health Service and Illinois Department of Public Health, Federal Security Agency, Washington, D. C., 1950.

NOTES

WORLD HEALTH ORGANIZATION

At its Fifth Session on October 23, 1950, the Expert Committee on Tuberculosis made several important recommendations. Some, having to do with the "Control of Tuberculosis in Countries with Undeveloped and Underdeveloped Programmes" are brought to the attention of readers of the REVIEW (Book Reviews, p. 119).

The Committee discussed the need for a single test dose of tuberculin for use with BCG vaccination programs and recommended that the screening Mantoux test dose be "5 Tuberculin Units (0.0001 mg. Purified Protein Derivative) and that the degree of induration be 5 mm. or more, at the end of three days." This corresponds to the recommendations for a single test dose in case-finding programs set forth in the 1950 Edition of DIAGNOSTIC STANDARDS and CLASSIFICATION OF TUBERCULOSIS except for two details. The latter reference states that the induration must be more than 5 mm. and that the test should be read forty-eight or seventy-two hours after the injection. The Expert Committee believed that further investigation is necessary to determine the dosage of tuberculin to be used in surveys of tuberculosis infection levels in a country.

The Committee also recommended that "the question of a uniform method of assessing the potency of tuberculin against the International Standard be referred to the Expert Committee on Biological Standardization for action." The many methods now in use give different results. The same Committee was asked to study the relative potency of wet and dry BCG vaccines.

The WHO Tuberculosis Research Office was requested to reassess the oral method of BCG vaccination.

Several specific recommendations were made concerning the functions of general hospitals in tuberculosis control. These are:

(a) Routine roentgenographic examination of all new patients in the wards or outpatient clinics; if the annual numbers are large, miniature radiography will be economical and effective.

(b) Allocate a reasonable proportion of their beds for the establishment of a tuberculosis service, using a separate block or section but, in any event, separate wards. This service should be under the control of specialists, possibly the same as those directing any associated tuberculosis dispensary.

(c) All cases of "sputum-positive" tuberculosis discovered in the general wards should be moved immediately to the special service. It is undesirable to nurse an "open" case in a general ward, particularly if children are there. However, care must be taken not to send persons with only a tentative diagnosis of tuberculosis into the same room as "sputum-positive" cases.

(d) Only nurses who are reactors to tuberculin should be allowed to care for the tuberculous patients. It is suggested that nonreactors to tuberculin be given BCG vaccination to enable them to work on such services.

(e) All hospital employees should be examined for tuberculosis prior to employment, and at reasonable intervals thereafter, by roentgenographic examination and, if indicated, by laboratory and clinical examinations.

(f) The tuberculosis services in the general hospitals should be used for teaching tuberculosis care and control to student nurses (and, if applicable, to medical students).

(g) Newly diagnosed cases of tuberculosis discovered in the general hospital should be reported to the local health officer so that arrangements may be made to examine all contacts.

(h) Whenever possible, tuberculosis dispensaries should be associated with general hospitals, unless tuberculosis dispensary facilities are available in the neighborhood.

(i) The above recommendations should apply also to hospitals for the mentally ill and mentally deficient, and to infectious disease hospitals. It is strongly urged that these hospitals set aside facilities for the care of the tuberculous, either as units in the hospital or, if the number of cases is large enough, as separate institutions.

Additional recommendations were made concerning the training of more aides to work under fully trained nurses, and more personnel to teach hygiene to the tuberculous and their families.

ANTIBIOTICS AND CHEMOTHERAPY

A new journal, *Antibiotics and Chemotherapy*, is being published by the Washington Institute of Medicine. The editor-in-chief is Henry Welch, Ph. D., and the editorial board includes more than sixty well-known international authorities. The new journal will publish articles concerning research and clinical developments in the field of antibiotics and chemotherapy.

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 64 JULY, 1951 ABST. NO. 1

CLINICAL STUDIES, TUBERCULOSIS

Massive BCG Injection.—Fourteen adolescent boys were mistakenly vaccinated by the intradermal or subcutaneous route with a dose of BCG which was meant for administration by scarification. The injected dose of BCG was 75 mg. (1 cc.). The amount usually absorbed by the scarification route is estimated to be 0.1 mg.; 750 times as much BCG was injected as is commonly used. According to the Institut Pasteur, this is a greater dose than has ever been given. Local reactions occurred after a few days except in 4 cases where there was a delay of three to four weeks. All the patients developed abscesses which ulcerated and formed fistulas. All the ulcers and fistulas healed completely after five to seven months. The only treatment was bland ointment and ultraviolet irradiation. No general reactions were observed. One of the 14 boys developed pulmonary infiltration of short duration following tonsillitis two months after BCG vaccination; gastric specimens did not contain tubercle bacilli. The appearance of this transient infiltrate after BCG was believed to be coincidental. All the other patients had negative roentgenograms on two occasions. Tuberculin tests were performed six months after vaccination. Only one of the boys showed a negative reaction.—*A propos de l'injection involontaire a 14 jeunes gens d'une dose de BCG 750 fois supérieure á la dose habituelle, J. Meunier, Rev. de la tuberc., 1950, 14: 1053.*—(*V. Leites*)

Gastric Tuberculosis.—Tubercle bacilli seldom invade the stomach. It has been suggested that the bactericidal effects of hydrochloric acid and the paucity of lymph follicles in the gastric wall are reasons for this rarity. The lesion usually is diagnosed as a malignant neoplasm since the common symptoms are epigastric distress, vomiting, loss of weight and strength, and hemorrhage. A palpable mass has been observed in nearly half of the cases and evidence of tuberculosis has been found elsewhere in the body in approximately half of the cases. The patient reported was a 74-year-old man with an "upset stomach" and weight loss. Physical examination revealed no lesions, but gastrointestinal roentgenograms showed an extensive irregular mass involving the proximal two-thirds of the stomach. Laparotomy revealed a firm, nodular, rubbery mass involving the cardiac portion of the stomach and firmly adherent to the pancreas. A lymph node adjacent to the lesion was excised and microscopic examination revealed caseous necrosis and giant cell formation. The patient died later and at autopsy there was a mass measuring 15 to 20 cm. extending from the cardia of the stomach almost to the pylorus. All surfaces of the stomach were involved but the bulk of the lesion was in the lesser curvature. There were several yellow caseous nodules in the omentum. There were calcified areas at the apices of the lungs and fibrous adhesions at both apices. On the diaphragmatic surface at the base of the left lung there were several small round lesions resembling tubercles. Microscopically, there was tuberculosis of the liver and spleen as well.—*Tuberculosis of the stomach: A case report, R. N. Sherman & R. L. Johnston, Gastroenterology, November, 1950, 16: 593.*—(*L. Hyde*)

Bronchoscopy in Tuberculosis.—Of 150 tuberculous patients bronchoscoped at the Department of Phthisiology in Algers, 110 had symptoms suggestive of endobronchial

tuberculosis. Only 3 of the 150 patients had no bronchoscopically detectable lesions; 80 had "accompanying bronchitis"; 67 had specific tuberculous lesions. Of the specific tuberculous endobronchial lesions, 47 per cent were found in men and 40 per cent in women. There was no difference in incidence between Algerians and Europeans. Most of the lesions were in patients aged 18 to 30 years. There was a relatively high incidence of stenosis and ulceration in persons more than 40, probably due to the duration of disease. The extent and localization of the parenchymous lesions were not always correlated with the degree and topography of the bronchial involvement. "Accompanying bronchitis" varied in severity with mucosal congestion, edema, infiltration, and easy bleeding. It seems arbitrary not to consider this endobronchial tuberculosis. It is of more functional than anatomical importance; bronchial paresis is frequently present and hinders expectoration despite hypersecretion. The specific tuberculous lesions were most frequent in the right upper lobe bronchus in men and in the left upper lobe bronchus in women. Ulcerations represented 50 per cent of all specific lesions; stenosis with and without ulceration was found in 34 per cent. Eleven patients (7.2 per cent) had bronchial fistulas most often located in the right upper lobe bronchus, trachea, and left stem bronchus in the vicinity of the tracheobronchial lymph nodes. They appeared as small openings of variable size and number. The adjacent parenchyma frequently showed infiltration with excavation and nodular dissemination. The course of these fistulas was not influenced by antibiotics. Streptomycin was given for inflammatory and ulcerative lesions with very definite improvement. *p*-Aminosalicylic acid (PAS), 14 gm. daily, alone or with streptomycin also gave very favorable results. It is not believed endobronchial ulcerations complicate the course of therapeutic pneumothorax if antibiotics are used. In 11 such cases, there were 2 instances of ballooned cavities and one bronchopleural fistula; in 16 cases of "accompanying bronchitis" without ulcerations, there were 3 ballooned cavities and one bronchopleural fistula. Stenotic lesions of the bronchi, however, were found to be responsible for a higher incidence of complications and to constitute a contraindication to pneumothorax.—*Constatations bronchoscopiques chés 150 tuberculeux pulmonaires adultes, A. Lévi-Valensi, A. Zaffran, & C. Molina, Semaine d. hôp. Paris, January 14, 1951, p. 171.*—(*V. Leites*)

Spontaneous Pneumothorax.—Benign idiopathic spontaneous pneumothorax and tuberculous spontaneous pneumothorax are distinct entities with different causes, clinical pictures, and mortality rates. Cases of spontaneous pneumothorax should be carefully observed and the type or cause determined. In a two-year period at the Birmingham Veterans Administration Hospital, 41 cases of benign idiopathic spontaneous pneumothorax and 10 cases of tuberculous spontaneous pneumothorax were observed. A comparison of these and of 35 previous patients reveals the following: (*1*) pulmonary infiltration on roentgenograms—benign, none; tuberculous, 100 per cent; (*2*) pleural adhesions —benign, none; tuberculous, 91 per cent; (*3*) pleural fluid above the level of the diaphragm—benign, 5 per cent; tuberculous, 54 per cent; (*4*) immediate hospital mortality—benign, none; tuberculous, 29 per cent; (*5*) clinical illness—benign, occasional; tuberculous, almost always; (*6*) fever—benign, occasional low-grade and never for more than seven days; tuberculous, common, usually prolonged; (*7*) aftercare required—benign, none; tuberculous, continued bed rest.—*Spontaneous pneumothorax: Contrast of the benign idiopathic and the tuberculous types, B. Hyde & L. Hyde, Ann. Int. Med., December, 1950, 33: 1373.*—(*T. H. Noehren*)

Steroids and Tuberculosis.—With a new and simple technique the urinary output of 17-ketosteroids was measured in 85 cases of pulmonary tuberculosis of varying severity. In all grave forms of the disease, the urinary excretion of 17-ketosteroids was markedly

diminished, being almost zero in the cachectic forms. Preliminary therapeutic trials with large doses of testosterone have given encouraging results (Authors' summary).—*17-Cétostéroïdes et tuberculose, R. Rivoire, G. Jonnesco, & J. Paszkowski, Presse méd., July 1, 1950, 58: 764.*—(*V. Leites*)

Autopsied Cases of Tuberculosis.—In a series of 500 consecutive autopsies on male military patients who died with a primary diagnosis of pulmonary tuberculosis, 369 were white, 123 were Negroes, and 8 were Indians. Although the average age for the entire series was 35 years, half of the group were younger than 30. Far advanced pulmonary disease with cavitation was present in an overwhelming majority. The average duration of the disease for white patients was four and one-half years but for Negroes was only one year and seven months. Pulmonary hemorrhage was the immediate cause of death either by exsanguination or suffocation in 54 patients (10.8 per cent), 12 of whom were Negroes. Empyema was present in 104 patients and right-sided cardiac dilatation or hypertrophy was found in about 205 patients. No extrapulmonary involvement was present in 54 patients among whom the average age was higher than that of the group as a whole. Amyloidosis was present in 35 of the first 290 patients who died between 1939 and 1943; among the remaining 210 patients who died between 1944 and 1947, amyloidosis was present in only one instance. The last part of the series contained a large number of young patients with fulminating disease of short duration. There was a significant correlation between patients with laryngeal, tracheal, and gastrointestinal involvement. Renal involvement was usually bilateral. Adrenal gland involvement was present in 14 per cent of the cases. Clubbing was present in 22 per cent, in many of whom the duration of the disease was less than one year.—*Study of five hundred autopsies in cases of tuberculosis, M. C. Davenport & H. M. Greenleaf, U. S. Armed Forces M. J., January, 1951, 2: 97.*—(*E. A. Riley*)

Cesarean Section Following Death from Tuberculosis.—A woman of eighteen who was pregnant was also undergoing treatment for pulmonary tuberculosis. During the end of the seventh month of her pregnancy, she suffered from a series of severe hemoptyses, one of which ended fatally. A Cesarean section was performed within five minutes of pronunciation of death. A viable baby was obtained.—*Successful post-mortem Cesarean section following death from pulmonary tuberculosis, M. Kronick, New England J. Med., December 14, 1950, 243: 953.*—(*A. G. Cohen*)

Combined Infection of Bone.—Coccidioidomycosis and tuberculosis of the same bone has not previously been reported. They are known to coexist in the same individual, either in the lungs or in separate bones. A patient with chronic pulmonary tuberculosis later developed disseminated coccidioidomycosis. Bone lesions appeared in both ankles; tubercle bacilli were cultured from the drainage; biopsies showed *Coccidioides immitis*. The tuberculosis was cleared by streptomycin. The coccidioidin skin test changed from negative to positive, this good prognostic sign paralleling the unusual improvement which the patient has shown after more than a year.—*Coccidioidomycosis and tuberculosis in the same bones, C. G. Fraser, S. E. Monroe, & J. E. O'Hare, Ann. Surg., January, 1951, 133: 116.*—(*W. H. Ochway, Jr.*)

Thoracoplasty Results.—In a series of 1,137 cases of pulmonary tuberculosis treated by thoracoplasty in Bruges, principally at Sijsele Sanatorium, spinal anesthesia was generally employed. Radical, selective, and extensive thoracoplasties were used, sometimes preceded by extrapleural plombage using muscle tissue. During the period 1937 to 1946, 85 per cent of the "good-risk" candidates operated upon made a satisfactory recovery; during the last two years of that period the percentage has risen to 94. Only 32 per cent of the patients ordinarily considered "poor risks" recovered satisfactorily. Results were progressively better in all pa-

tients who survived three years. Physiologic, economic, and social adjustments were as satisfactory among patients originally considered "poor risks" as among the "good risks." Irremediable right heart failure, when it occurred, usually appeared in the first few years after operation.—*Rapport sur 1157 cas de tuberculose pulmonaire traités par thoracoplastie, à Bruges, depuis 1926, L. DeWinter, Acta tuberc. belg., November, 1950, 41: 169.*—*(A. T. Laird)*

Thoracoplasty with Lucite Balls.—Lucite balls are placed in the operative area after the first-stage thoracoplasty. The balls are removed at the second stage. The procedure has the advantage of improving the collapse, of facilitating the second stage by preventing the formation of adhesions between the superficial and deep layers, and especially of fixing the apex in the position of collapse so that no considerable pulmonary re-expansion develops subsequently. In patients with serious lesions of the apex, Lucite balls have been inserted again during the second stage and left in place for several months until the development of bony regeneration has established the collapse. This technique of thoracoplasty gives better results, limits the extent of rib resections downward, and prevents impairment of function. This experiment was carried out on 49 patients; 23 had resections of 5 ribs, 16 of 6 ribs, and 2 of more than 6 ribs. No complications attributable to the plombage were observed. The results obtained were better than with any other type of thoracoplasty (Author's summary).—*La thoracoplastie avec plombage temporaire aux billes de lucite, H. Joly, Presse méd., November 25, 1950, 58: 1324.*—*(V. Leites)*

Bronchostenosis Repaired with Dermal Grafts.—Tuberculosis of the trachea and bronchi is more frequent in women, and stenosis more often occurs in the left main bronchus. Only the upper end of a stenotic bronchus can be seen but, if the tuberculosis appears to be quiescent there, the remainder of that bronchus is likely to be healed. While stenosis of a bronchus is usually in a uniform state of healing the bronchi beyond it may be actively diseased. Because of the more favorable pathologic changes and its surgical accessibility, the posterior membranous surface of the trachea and bronchi is the most suitable site for surgical attack. In many patients tuberculosis produces a deformity of the air passage with chronic disability for which most patients willingly submit to excisional surgery. This relieves their symptoms but deprives them of good lung tissue. In 4 patients, stenosis was relieved and functional lung tissue was saved by longitudinal incision of the stenotic bronchus and closure of the elliptical defect with a dermal graft. The graft was stiffened by lacing with 28-gauge stainless steel wire. A year after operation the patients were all free of symptoms of stenosis.—*Plastic reconstruction of tuberculous bronchostenosis with dermal grafts, P. W. Gebauer, J. Thoracic Surg., April, 1950, 19: 604.*—*(R. E. MacQuigg)*

"Round Bodies" in Tuberculosis.—Determination of the exact nature of the "ring bodies" or "round shadows" seen in roentgenograms of the lung is of considerable practical importance. They represent filled tuberculous cavities more frequently than has been commonly supposed. Diagnosis is difficult if they are first noted after the cavity has been completely filled, since they must be distinguished from malignant metastases, gummata, mycoses, abscesses, fibromata, encysted effusions, very large primary tuberculous foci, or tuberculomata. A tuberculous origin may be suspected from a history of contact with infectious tuberculosis, or of hemoptyses, pleurisy, pneumothorax, or other symptoms suggestive of the disease. The largest primary focus observed measured 2.4 by 3 cm.; the enlargement of regional lymph glands renders recognition of such foci comparatively easy. Assmann's subclavicular infiltrations usually do not appear until long after the primary infection. Occasionally small calcifications are found in

Assmann lesions which do not entirely disappear; sometimes the foci do not clear but slowly progress to caseation and ulceration. A tuberculoma may become very large and encapsulated. Surgical intervention may be indicated; either exeresis or Monaldi drainage of the confluent softened interior may be necessary. The relationship of the round bodies to the bronchi is an important diagnostic criterion and may be determined by tomography, as in 49 of the authors' 148 cases of filled cavities. Such cavities may be discoid or have irregular contours. Bronchoscopy may help to determine the connection of filled cavities with the bronchi draining them. Filled cavities should be treated by promotion of drainage through appropriate medical treatment, collapse therapy, or surgical removal of the affected portion of the lung.—*Les images rondes de la tuberculose pulmonaire, A. Bernou & J. Tricoire, Poumon, September, 1950, 6: 425.—(A. T. Laird)*

Tuberculosis with Normal Roentgenograms.—Schmidt has emphasized that 47.3 per cent of the cases of infectious tuberculosis could be recognized a year earlier if the sputum were examined carefully. In two years at the University Hospital in Brno, tubercle bacilli were found in 179 cases; 155 of the cases were easily diagnosed. In 10 cases, tuberculosis was not suspected initially but was later diagnosed. The remaining 14 patients had no pulmonary lesions; 6 of them had had exudative pleurisy previously; 2 others had had erythema nodosum. Another 5 patients were admitted with such complaints as slight fever, cough, or weight loss; 4 of them had had hemoptysis. The remaining patient had coughed persistently for a few weeks; roentgenograms were always negative but bronchoscopy revealed a tuberculous ulcer in the right main bronchus.—*Positive findings of tubercle bacilli in roentgenographically negative cases (Czech), A. Ningerova, Lék. listy, February 1, 1951, 6: 77.—(J. Ilavsky)*

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Hemoptysis.—In 400 patients with hemoptysis, roentgenograms were normal and the sputum, if present, was negative for tubercle bacilli; no diagnosis could be made initially. In 294 of the 400 (73.5 per cent), bronchoscopy demonstrated the cause of the bleeding; 71.75 per cent showed changes in the bronchial mucosa. In 6 cases (1.5 per cent), carcinoma of the bronchus was present. There was one case of nontuberculous ulceration. In 8.5 per cent the bronchoscopic aspect of the mucosa was equivocal and a definite interpretation was not possible; in the remaining 18 per cent, bronchoscopy was entirely negative. Various forms and degrees of bronchitis were responsible for 59.7 per cent of the bleeding. There was redness, thickening of the mucosa, hypersecretion, and modification of the local sensitivity. Biopsies confirmed the inflammation of the mucosa and showed metaplasia of the bronchial glands which were swollen with mucus. In 114 cases (28.5 per cent), the bronchitic changes were circumscribed. In addition there were 17 cases of localized bronchitis which were in close relationship to hilar calcifications.—*Les hémoptysies sans cause apparente (a propos de 400 cas), J. M. Lemoine & F. Finet, Presse méd., December 9, 1950, 58: 1370.—(V. Leites)*

Bronchial Abnormalities Simulating Tuberculosis.—With the increasing use of the mass roentgenologic chest survey, many heretofore unseen bronchopulmonary shadows are being uncovered in apparently healthy individuals. Bronchial disease or bronchial anomalies in the upper lobes may cast radiographic shadows simulating pulmonary tuberculosis. Bronchiectasis of the upper lobe is a frequent result of inactive reinfection tuberculosis or a sequela of healed primary tuberculosis. The radiographic criteria for the diagnosis of upper lobe bronchial abnormalities differ little from those for the same conditions in the basal regions. There is a web-like process or honeycombing with small irregular areas of translucency de-

lineated by fine fibrous strands or lines; sometimes the shadows of the bronchial walls run diagonally across the upper lobe and disappear abruptly into the parenchyma. In most instances the abnormal shadows seem to have their origin in, and are continuous with, the root shadow. Infiltrates are much more likely to indicate tuberculosis than upper lobe bronchial involvement. Where the latter is suspected the diagnosis is established by upper lobe bronchography. Upper lobe bronchial abnormalities change very little radiographically in the course of years following their accidental discovery in the mature person. As a rule they produce little or no disability.—*Upper lobe bronchial abnormalities simulating significant pulmonary tuberculosis, L. Schneider, Radiology, September, 1950, 55: 390.*—(*W. J. Steininger*)

Primary Atypical Pneumonia.—A review of 67 cases of primary atypical pneumonia observed in a general hospital emphasizes the variety of clinical patterns attributable to this disease. The illnesses ranged in severity from an obscure fever to a severe pulmonary infection with circulatory collapse. Not only did this syndrome mimic tuberculosis and other forms of pneumonia but, particularly in older individuals, it was confused with cardiac decompensation, emphysema, and chronic bronchitis associated with other febrile illnesses. Equal numbers of patients had onsets resembling a common cold, tracheobronchitis, or "grippe." The most common symptoms were cough, malaise, fever, sore throat, chilliness, anorexia, and headache. The average patient had been sick for ten days before admission and had a maximal temperature on the eleventh or twelfth day of disease. Seventy-nine per cent of the patients were afebrile by the end of the third week of illness. On admission, 50 per cent of the patients had pulmonary signs which corresponded in extent to the infiltration shown by roentgenograms. The other 50 per cent showed discrepancies between signs and roentgenograms, almost as many patients exhibiting predominance of signs as exhibited predominance of infiltration on roentgenograms. In 10 cases the correlation between physical findings and roentgenographic changes remained poor throughout the illness and in most of these cases the signs spread widely while the roentgenographic picture remained unchanged. The average duration of abnormal pulmonary signs after onset was three weeks, but 15 per cent of the patients had such signs for more than four weeks. The level of the leukocyte count on admission was related to the duration of disease. Two-thirds of the patients had counts of less than 9,000 on admission; two-thirds had counts of more than 9,000 during hospitalization. An increase in leukocyte count most often accompanied spread of the pulmonary lesion. Counts as high as 35,000 may occur in primary atypical pneumonia in the absence of secondary bacterial infection. Fourfold or greater rises in the titer of cold hemagglutinins, of streptococcal MG agglutinins, or of both occurred in 43 cases (65 per cent) in direct correlation with the severity of the illness as measured by duration of fever and extent of pulmonary involvement (Authors' summary).—*Clinical variations in primary atypical pneumonia, W. S. Jordan, Jr., R. W. Albright, F. H. McCain, & J. H. Dingle, Am. J. Med., January, 1951, 10: 3.*—(*T. H. Noehren*)

Atypical Pneumonia.—Atypical pneumonia is diagnosed with increasing frequency since Rieman's work in 1938. All atypical pneumonias are not caused by the same agent and different etiologic agents probably are responsible for the clinical and laboratory differences frequently noted. Implicated in atypical pneumonia have been the virus of herpes, psittacosis, influenza, Newcastle, lymphocytic meningitis, the *Rickettsia* of Q-fever, and possibly *Streptococcus viridans;* less than 20 per cent of atypical pneumonias can be attributed to these agents. During the late winter of 1949 and the spring of 1950, 61 cases were studied. Most of the patients were ill for four to ten days before entering the hospital. The fever was usually of short duration, 59

per cent of the patients having fever for less than five days. The morbidity sometimes was prolonged, 14 per cent not having completely recovered in 30 days. The chief symptoms were fever, cough, chest pain, anorexia, malaise, and chills. Dyspnea, headache, and weakness were less frequent and hemoptysis was infrequent. Physical findings often were difficult to elicit or were minimal. In 8 cases, physical findings were negative even after roentgenograms had demonstrated infiltration in the lungs. More than half of the patients entered the hospital with leukocytosis and only 4 patients had leukopenia. Immunologic studies included Hirsch's chicken-cell agglutination using 4 strains of influenza virus, Newcastle virus agglutination, complement fixation for Q-fever, cold agglutinins, and heterophile agglutination. Although 21 patients had high titers for influenza, the control group of patients had as many high-titer sera as the atypical pneumonia group. This would seem to indicate that influenza played no etiologic role in the cases studied. There was not a single positive reaction to the Newcastle virus. Only 6 patients had a positive test for cold agglutinins; only one of these had a high titer. A significant titer or an increasing titer for heterophile antibodies was not found in any case. Serology studies for the most part have not been helpful, and cold agglutinins appeared only rarely in these patients.—*Studies of atypical pneumonia, R. O. Muether & A. H. Ishii, J. Nat. M. A., January, 1951, 43:* 7.—*(B. Hyde)*

Primary Staphylococcic Pneumonia.—Secondary staphylococcic infection of the lung is part of the picture of pyemia. Primary infection occurs sporadically in infants and young children and as a complication of influenza in older persons. The mortality is very high, particularly in the young. Several clinical types are seen. During the influenza pandemic of 1918 a fulminating type was seen. After three to four days of influenza the patient's condition suddenly became critical and he died. Less severe is the acute pneumonic type. In a patient who is suffering from ordinary influenza the symptoms, instead of disappearing, persist. After one to two weeks, cough and expectoration appear. An abscess may or may not develop. Empyema appears in 10 to 30 per cent of the cases. The white blood count reaches 15,000 to 20,000. There is usually complete recovery. In some, a residual uninfected cyst remains. Early roentgenograms show scattered and localized areas of bronchopneumonia. The initial opacities coalesce, giving a solid lesion; then multiple cavities appear, some of which may become very large. Often there is a bronchogenic spread. The consolidation resolves leaving a thin-walled cavity which contains very little fluid and finally disappears. Both penicillin and sulfonamide drugs give excellent results. Abscesses should not be operated upon. Likewise, aspiration and penicillin installation are adequate treatment for the complicating empyema. The prognosis is excellent. There was no death in 10 cases.—*Primary staphylococcal pneumonia, M. O. J. Gibson & J. R. Belcher, Quart. J. Med., January, 1951, 20:* 43.—*(A. G. Cohen)*

Suppurative Pneumonia.—Suppurative pneumonia is an inflammatory consolidation of the lung which proceeds in whole or part to suppuration. It can occur in the course of certain specific pneumonias. In other cases, a mixture of organisms is recovered, none of which are ordinary invaders of the lung. In pneumococcal lobar pneumonia, lung abscess is rare. Occasionally during resolution translucent areas are seen but soon disappear; this phenomenon is not accompanied by the production of sputum. In staphylococcal pneumonia, abscess formation is an important feature. The onset is insidious. There is a relatively slow pulse. The roentgenogram shows scattered opacities; the sputum is purulent but not foul. The disease may be rapidly fatal. In a less virulent type the fever diminishes but the expectoration increases, and single or multiple abscess cavities appear. These characteristically are empty or almost so and have a thin-walled, soap-bubble appearance. They lie in the midst of apparently normal lung, may perforate into the pleura, and may be-

come chronic. The infection may burn itself out leaving a cyst. Staphylococcal abscesses may also appear in the course of pyemia. They may be multiple, small, and empty. The treatment for both types is strictly medical using large doses of penicillin. Friedländer's pneumonia usually is severe; the acute type has a high fatality rate. There is also a chronic form which runs a course similar to tuberculosis. Abscess formation within areas of massive consolidation is common. Streptomycin therapy is effective. Other specific pneumonias are caused by *Entameba histolytica*, histoplasmosis, coccidioidomycosis, and actinomycosis. In bronchogenic carcinoma, abscess formation is caused either by breakdown of the growth, especially in the squamous cell type, or by infection secondary to bronchial obstruction. Nonspecific suppurative pneumonias vary in severity from acute lung abscess to benign aspiration pneumonia with mild respiratory symptoms and transient radiographic shadows. These shadows result from the aspiration of mucus which causes obstruction of bronchi or bronchioles. They are seen particularly in patients with chronic bronchitis, asthma, or chronic abnormalities of the upper respiratory tract. The inflammatory reaction is slight and recovery is rapid. There is strong evidence to indicate that acute lung abscess results from aspiration. A less severe condition is suppurative pneumonia of intermediate severity, without cavity formation. The distinction between fetid and nonfetid sputum cannot be made with accuracy and the distinction has no particular bearing upon treatment. It has been shown that anerobic spirochetal organisms are responsible for lung abscess in certain cases. Once established, the pulmonary suppuration may become chronic. Chronic nonspecific suppurative pneumonia is the term used by the author to describe that type of pneumonia characterized by long-standing production of purulent sputum having a mixed flora, by areas of consolidation in the lungs, and often by abscess cavities. There is a great preponderance of male patients. Of 57 cases, 28 were followed long enough to be analyzed. There was dental sepsis in 7, dental extraction in 2, operation under general anesthesia in 2, chronic bronchitis in 5, other causes in 3, and no apparent cause in 5. In some cases, there was an acute onset and a cavity was seen in the first three weeks; this is the typical course of an acute lung abscess. In others, the onset was acute with pulmonary consolidation but no abscess formation in the first three weeks. In others, the onset was more gradual. In all cases the initial fever fell but, after a period of normalcy, there were flurries of temperature elevation associated with sputum retention. Many of the patients felt relatively well. The amount of expectoration was considerable in most cases; the presence of fetor was variable. Hemoptysis was frequent; clubbing of the fingers was almost universal. The white blood counts were slightly elevated. Sputum examinations showed a mixed flora, but no tubercle bacilli. Bronchoscopy was useful in (*1*) confirming the absence of obstructive bronchial lesions, (*2*) demonstrating localised redness and edema which is of value for localization, and (*3*) suctioning of pus for examination. Radiographically, initially there was consolidation with or without abscess formation. At the onset, the process was segmental but later readily spread to contiguous and even distal areas. Cavitation appeared at any stage. There were frequent recrudescences associated with spread of the disease. Simultaneously, there often was clearing of other areas usually with evidence of fibrosis. Bronchograms were of no value at this stage. Friedländer's pneumonia may run a similar course but tuberculosis at this stage is usually less productive of sputum. Differentiation from carcinoma may be difficult. Bronchiectasis may be differentiated by history. The early treatment consists of postural drainage and penicillin administration. This may lead to recovery in some though a later bronchogram will show bronchiectasis. The progress of the disease is checked so that the patient's condition improves sufficiently to permit surgery. In extensive cases, which cannot be operated upon, the patient is made more comfortable. External drainage is not done. The definitive

surgical treatment is resection of the involved areas.—*Suppurative pneumonia, H. Nicholson, Lancet, November 18 and 25, 1950, 2: 549 and 605.*—(*A. G. Cohen*)

Cryptococcosis.—Cryptococcosis or torulosis is a chronic or subacute infection that may involve any part of the body, has a special predilection for the brain and meninges, and is considered to have a high mortality rate. In early cases of pulmonary involvement alone, the patients usually are asymptomatic but may complain of a slight and usually nonproductive cough. Clinical symptoms and physical signs become evident when meningitis, which is the invariable cause of death, supervenes. It has been stated that the majority of patients die within six months of the onset of symptoms, but if they survive this initial acute phase they may live from two to four years. The diagnosis depends on the isolation of the yeast from the sputum or spinal fluid, with proof of pathogenicity by animal inoculation. The diagnosis should be considered in any case of chronic meningitis and in any patient with roentgenographic evidence of pulmonary infiltration without apparent cause. A 30-year-old white male was admitted to the hospital because of roentgenographic evidence of a pulmonary lesion. His only complaint was that one month before admission he had had pain for one day in the right lower portion of his chest. This pain did not return and there was no history of cough, expectoration, weight-loss, anorexia, fatigue, sweating, or fever. A roentgenogram of the chest revealed a circular area of homogenous density, about 5 cm. in diameter, in the right middle lung field which on the lateral projection was seen to be in the right middle lobe. Subsequent roentgenograms showed no significant change in the appearance of the lesion. The roentgenogram of the chest and the finding of *Cryptococcus neoformans* in the sputum were the only indications of cryptococcal infection. Sensitivity tests showed the organism to be sensitive to polymyxin *in vitro*, but on treatment the infection did not respond. Penicillin, streptomycin, sulfadiazine, and potassium iodide were all used to tolerance dosage without success. The patient died with meningitis fourteen weeks after admission to the hospital. It is suggested that patients showing pulmonary involvement of localized nature, in the absence of systemic spread, be given the benefit of surgical removal of the involved area of the lung.—*Cryptococcosis: Review of the literature and report of a case with initial pulmonary findings, H. E. Ratcliffe & W. R. Cook, U. S. Armed Forces M. J., September, 1950, 1: 957.*—(*T. H. Noehren*)

Q-Fever.—Between the years 1943 and 1945 several small epidemics of Q-fever were seen among the American solidiers in Europe. In the years 1939, 1941, and 1942 a similar epidemic, called "Balkangrippe," had been observed among the German occupation troops in the Balkans. In 1946 the first Q-fever cases were described in Switzerland. Since then this disease has been seen in all European countries with the exception of the Scandinavian countries.—*Ueber das Q-Fieber, Gino Meldolesi, Wien. klin. Wchnschr., January 5, 1951, 63: 5.*—(*G. C. Leiner*)

Infectious Mononucleosis.—The roentgenologic findings of infectious mononucleosis consist of visibly enlarged hilar lymph nodes. The enlargement of these nodes may not be accompanied by external adenopathy. It is now proved, as had been postulated, that the glandular involvement may be confined to deep-seated, mediastinal and mesenteric nodes. More commonly there is general adenopathy, and enlargement of the internal nodes may only precede the palpatory evidence of glandular swelling. Enlargement may persist for months or years and become a roentgenologic enigma. These mediastinal lymph nodes are of sufficient size to be visible through and beyond the vascular hilar shadow. They are discernible on the lateral view as well as on the posteroanterior view. In 4 cases they were close enough to the pulmonary vessels and the waist of the heart to simulate a congenital heart lesion. In no case did the nodes form masses suggestive of lymphoblastoma. Fine opaque

strands were observed emanating from the hilus, suggestive of increased bronchovascular markings. In some cases they were so dense and surrounded by spotty infiltrations as to be interpreted as atypical pneumonia. The hematologic and serologic tests proved them to be manifestations of infectious mononucleosis.—*The roentgenological aspect of infectious mononucleosis, J. Arendt, Am. J. Roentgenol., December, 1950, 64: 950.*—(*T. H. Noehren*)

Gaucher's Disease.—Two brothers, four and five years old, developed jaundice, hepatomegaly, and splenomegaly. The roentgenograms of both boys showed micronodular dissemination throughout both lung fields. Two years later one of the brothers developed small axillary nodes; biopsy revealed a completely modified structure of the node with lobulation into a dozen circumscribed areas separated by vessels and connective tissue. There was hyperplasia of histiocytes and reticulocytes which were overloaded with lipids. Although no typical Gaucher cells were seen, the histologic aspect resembled most closely that of lipoid diseases of the reticulo-endothelial system, in particular Gaucher's disease. The disseminated pulmonary lesions are interpreted as lipoid deposits in the reticulo-endothelial system of the lung. The children were followed for eight years, during which time there was no change in the appearance of the roentgenogram.—*Contribution à l'étude des localizations pulmonaires de la maladie de Gaucher, L. Grandmaison, Presse méd., January 24, 1951, 59: 85.*—(*V. Leites*)

Syphilis of the Lung.—A 30-year-old woman with a history of treated syphilis of three years' duration was hospitalized with fever between 99° and 100°F. and hemoptysis. Roentgenograms showed a massive consolidation in the right mid-lung field which rapidly developed into a large oval cavity without a fluid level. Sputa and gastric contents were negative for tubercle bacilli. The sedimentation rate was 40 to 70 mm. per hour; there were 8,000 leukocytes; and the Mantoux test was positive. Because of the history of syphilis, the low-grade fever, the lack of bacteriologic evidence of tuberculosis, and the absence of expectoration, the diagnoses of lung abscess and pulmonary tuberculosis were discarded and a tentative diagnosis of excavated gumma of the lung was made. Cyanide of mercury was administered and there was rapid disappearance of the cavity on standard and tomographic roentgenograms. Since the patient was a prostitute the possibility of a syphilitic reinfection was considered and the case interpreted as a syphilitic Koch phenomenon.—*Phenomène de Koch syphilitique au niveau du poumon, P. Simonin, Girard, & Neully, Presse méd., December 25, 1950, 58: 1482.*—(*V. Leites*)

Uremic Pulmonary Changes.—Of 5 cases of pulmonary changes associated with uremia, 4 were examined pathologically. The roentgenologic findings were extensive fluffy shadows in the inner lung zones. These findings are frequently out of proportion to the general appearance of the patient who may show only moderate dyspnea and few abnormal physical signs in the chest. The outstanding microscopic features of the uremic lung in these cases were (*1*) the thickened alveolar septum, which frequently showed pronounced congestion of the alveolar capillaries; (*2*) fibrinous alveolitis, which showed various stages of hyalinization of the intra-alveolar exudate; and (*3*) the presence of a pseudohyaline membrane.—*Pulmonary changes in uremia, H. E. Bass & E. Singer, J.A.M.A., November 4, 1950, 144: 819.*—(*H. Abeles*)

Pneumonitis from Chromic Acid.—Chromic acid is used primarily for chrome plating. In the anodic operation, the metal to be coated is immersed in the chromic acid bath. Electrolytic oxidation causes the oxide to be formed as a film on the metal when the electric potential is gradually raised. As the temperature of the solution is elevated, fumes are liberated and contain particles of chromic acid; from these baths, workers may inhale varying amounts of the substance. The inhalation of

chromium trioxide is known to cause pulmonary hyperemia and inflammation. The effects on the mucosa of nasal passages and the cartilaginous septum have been reported on many occasions. Two cases illustrate the acute effects following the inhalation of massive amounts of chromic acid mist. These patients had been exposed to the acid for periods of one to four days. The first patient had pulmonary congestion and edema; the initial roentgenogram showed marked congestive changes throughout both lung fields. At bronchoscopic examination the surface of the entire visible tracheobronchial tree was hyperemic and somewhat edematous. All subsidiary bronchial orifices were normal, and the aspiration specimens were normal. After a stormy sixteen-day course, the patient was discharged in good condition but continued to have infrequent chills, cough, and mild anterior chest pain. The second patient showed no immediate ill effects from inhalation of the fumes but, during the following three or four days, he became hoarse with a cough productive of whitish mucoid sputum. He felt well and able to work, but during the following three months he became anorexic and gradually lost weight. He was admitted to the hospital because of sharp pain in the right upper abdominal quadrant and severe, sharp chest pain, precipitated and aggravated by a chronic cough. Splinting of the right side of the chest was noted and a pleural friction rub was present. His course was satisfactory, and he was discharged after two weeks at which time his chest was clear. Roentgenograms revealed only pleural thickening at the left apex. Bronchoscopic examination showed mucous "pearl" secretions which were aspirated from the left main stem bronchus. At that time there was no evidence of bronchial disease. These cases demonstrate that the deeper pulmonary structures may show severe damage from chromic acid mist while the nasal mucosa shows only mild hyperemia.—*Acute pulmonary complications following inhalation of chromic acid mist, J. B. Myers, A.M.A. Arch. Indust. Hyg. & Occup. Med., December, 1950, 2: 742.*—(*T. H. Noehren*)

Histoplasmin Tests in Children.—Histoplasmin skin tests were done on 500 infants and children who were admitted to four hospitals in St. Louis, Missouri. A positive reaction was found in 14.6 per cent. The incidence of positive tests increased rapidly up to the age of ten years and was twice as high among males as females. Most of the positive reactors came from rural areas near St. Louis, in contrast to the predominantly urban origin of the concurrent general admissions. Eighteen positive histoplasmin reactors negative to tuberculin had chest roentgenograms; half had pulmonary and hilar calcification, and another quarter had hilar lymphadenopathy. The illness for which the positive reactors were admitted was predominantly chronic while the negative reactors usually had some sort of acute disease.—*Results of histoplasmin skin testing in children from the St. Louis, Mo. area, J. F. Lynch & E. B. Alpern, J. Pediat., January, 1951, 38: 51.*—(*W. H. Oatway, Jr.*)

Erythema Nodosum and Boeck's Sarcoid.—Erythema nodosum is often a manifestation of primary tuberculosis occurring generally when the patient first develops a sensitivity to tuberculin. The opinion that this disorder is of rheumatic origin is disappearing. The eruption is also seen as a sensitivity reaction to both sulfonamide drugs and streptococcal infections and has been associated with meningococcal septicemia, *Coccidiodes immitis* infections, and other diseases. In 3 typical cases erythema nodosum was associated with sarcoidosis. No morphologic confirmation of the clinical diagnosis was obtained in any of the 3 cases.—*Erythema nodosum as initial manifestation of Boeck's sarcoidosis, F. E. Crawley, Brit. M. J., December 16, 1950, No. 4693: 1362.*—(*E. A. Riley*)

Aminophylline for Emphysema.—A group of cases of emphysema without asthma was studied. In normal subjects, administration of 0.5 gm. of aminophylline orally resulted in no change in the total lung volume and its subdivisions. In the emphysema group, determinations before, and one-half hour after, ad-

ministration of the drug were identical when the patient was in the recumbent position. In the sitting position, there was slight reduction in the total lung volume, functional residual air, and residual air. Tidal air tracings were unaltered. It is concluded that oral aminophylline has no value in emphysema without bronchospasm.—*Effect of aminophylline in emphysema, A. G. W. Whitfield, W. M. Arnott, & J. A. H. Waterhouse, Lancet, March 3, 1951, 1: 494.*—(*A. G. Cohen*)

Pulmonary Agenesis.—Pulmonary agenesis may vary in degree from complete absence of the bronchus, pulmonary tissue, and pulmonary vessels of all or part of a lung to a hypoplasia of a pulmonary segment with normal bronchi and pulmonary vessels. It is often associated with other congenital abnormalities, particularly of the heart. Either or both lungs may be affected. It has been encountered at all ages up to 72 years and equally in both sexes. There are no symptoms. Clinically, there may be flattening of the affected side of the chest. The physical signs are those of pulmonary collapse. Diagnosis is established by bronchography and sometimes bronchoscopy. The author reports 4 cases. In recent years the diagnosis has been made clinically in approximately 20 cases, including 3 of the author's. In many cases there is gross displacement of the heart and mediastinal contents. Clubbing is not seen. The condition must be differentiated from atelectasis, which is less persistent and usually does not cause asymmetry. The prognosis depends mostly upon the associated lesions. The critical period is the first six months of life. During this period, 21 of 50 patients died; only 18 lived to be five years old.—*Pulmonary agenesis, F. S. W. Brimblecombe, Brit. J. Tuberc., January, 1951, 45: 7.*—(*A. G. Cohen*)

Bronchial Rupture.—External injury to the chest which results in rupture of a bronchus is usually fatal. Twenty cases of survival have been reported but early surgery was done on only 2. Sanger has suggested that thoracotomy be done for any tension pneumothorax which cannot be controlled by needle or catheter. A "closed" injury to the chest rarely results in bronchial rupture, and no record can be found where surgery was done for its relief. A ten-year-old boy was hit by an automobile and sustained a "closed" injury with tension pneumothorax. It was necessary to do a right thoracotomy, with resultant relief. A large bronchial tear was found and closed. Laceration of the upper and lower lobes was present; a portion of the former was nearly sheared off, and was resected. All tears were closed, and recovery was complete. The injury to the lung structures was not due to the several broken chest bones, with a fragment of one rib chipped free into the pleural space, but to the excessive distortion produced by severe external violence to the elastic thoracic cage of a child.—*Rupture of the bronchus following closed injury to the chest.—J. G. Scannell, Ann. Surg., January, 1951, 133: 127.*—(*W. H. Oatway, Jr.*)

Pneumothorax from Secondary Sarcoma.—A 51-year-old woman was shown at autopsy to have bilateral spontaneous pneumothoraces secondary to pulmonary metastases from a leiomyosarcoma of the uterus. There was marked necrosis of the pulmonary lesions which in the right lung had caused extensive ulceration of the visceral pleura. The development of a bronchopleural fistula following necrosis of a subpleural nodule was the probable etiologic mechanism; rupture of a distended peripheral alveolus distal to a bronchial ball-valve obstruction seemed less likely. The apparently rare association of pneumothorax secondary to metastatic pulmonary disease is surprising.—*Spontaneous pneumothorax from secondary sarcoma of lung, A. B. Shaw, Brit. M. J., February 10, 1951, No. 4701:278.*—*E. A. Riley*)

Broncholithiasis and Broncho-Esophageal Fistula.—The authors present a case of broncholithiasis associated with a broncho-esophageal fistula, and in reviewing the literature find a report of only one similar case. Probably the inflammatory reaction surrounding a

tuberculous peribronchial lymphadenitis had involved the esophageal wall. As cicatrization and calcification of the glands progressed, a traction diverticulum had formed. The fistula may have developed as the result of reactivation of the periglandular inflammatory reaction with ulceration and erosion into the esophagus and bronchus; it may have followed the development of an ulcerative esophageal diverticulitis with suppuration extending through the calcareous node and eventually eroding into the bronchus. The diagnosis of broncholithiasis was established by the expectoration of calculi. The fistula was unsuspected until a pneumonectomy was performed because of bronchoscopic findings of a mass suggesting carcinoma. This mass was later proved to be chronic inflammatory and vascular granulation tissue.—*Broncholithiasis and broncho-esophageal fistula, H. M. Kidd & E. Christopherson, Canad. M. J., February, 1951, 64: 142.*—(*E. A. Riley*)

Benign Mediastinal Tumors.—Benign mediastinal tumors must be differentiated from those that arise outside the mediastinum and intrude upon it: (*1*) From the cervical region. Thyroid adenomata may be substernal extensions of cervical goiters or truly aberrant thyroid tissue. The former are characterized by tracheal compression and continuity with the neck lesions and are easily diagnosed. (*2*) From the bony thorax, chondromas or chondrosarcomas. (*3*) From below the diaphragm, hernias, especially through the foramen of Morgagni. (*4*) From the heart and great vessels, aneurysmal dilatations. Fluoroscopy, laminagraphy, kymography, and angiography all may help in diagnosis. Occasionally exploratory thoracotomy may be necessary. (*5*) From the spinal cord, meningoceles. Most dermoids lie anteriorly. Bronchogenic cysts lie anywhere in the upper paratracheal region or along the larger bronchi. Leiomyomata of the esophagus can be demonstrated by a barium swallow. Neurogenic tumors usually lie posteriorly and paravertebrally; sometimes enlargement of an intervertebral foramen can be demonstrated. Lesions in the anterior cardiophrenic angle may be pericardiocelomic cysts, cystic lymphangiomata, dermoids, partial eventrations of the diaphragm, and hernias through the foramen of Morgagni. Barium enema and diagnostic pneumothorax aid in the diagnosis. The diagnosis of a mediastinal tumor is the indication for surgical excision. The mortality is very low. In the authors' series there was one operative death in 31 cases.—*Diagnostic and therapeutic problems in benign mediastinal tumors, G. E. Lindskog & H. W. Kansel, New England J. Med., February 15, 1951, 244: 250.*—(*A. G. Cohen*)

Circumscribed Intrathoracic Lesions.—In a series of 44 cases with single circumscribed intrathoracic densities, each case was referred for an exploratory thoracotomy if malignancy could not be ruled out with certainty. The work-up consisted of a careful history, physical examination, review of previous roentgenograms, fluoroscopy, roentgenograms including tomography, tuberculin test, skin tests for fungi, and examination of the sputum and gastric contents for tubercle bacilli. Bronchoscopy, angiocardiography, and roentgenograms of the gastrointestinal and genitourinary tracts were often done. In most cases, these studies were nonrevealing. The most valuable single procedure was tomography; the presence of calcification indicated tuberculosis or hematoma. Operation was performed in 21 cases. The procedure ranged from excision to pneumonectomy. There was one operative death and 2 serious postoperative complications. Pulmonary malignancies were found in 7 cases, solitary metastasis in one, tuberculosis in 5, benign tumors in 3, chronic lung abscess in 2, and lipoid pneumonia, pericardial cyst, and bronchiectatic cyst in one each. Ten patients on whom operation was not done for one reason or another were followed for at least a year. One is dead of carcinoma and 4 others are known to have it. In 3 there has been no change in the size of the lesion after twelve to thirty months. In 2 there was an increase in size followed by a stationary period.—*Single circumscribed intrathoracic densities, H. Abeles*

& D. Ehrlich, New England J. Med., January 18, 1951, 244: 85.—(A. G. Cohen)

Hamartoma of Lung.—The literature contains reports of approximately 100 cases to which the authors add 9 of their own. The lesion may occur in any part of the lung or may be endobronchial. It varies in size from that of a hemp-seed to a mass which occupies the whole pleural cavity. It is whitish yellow in color and globular or slightly oval in shape. It has the consistency of cartilage. Histologically, the cartilage is disposed in lobules which are separated by loose, richly cellular vascular connective tissue. The condition is always benign. In 8 of the cases, there was deposition of calcium in the cartilage. The lesion is probably a congenital malformation. There is no evidence of malignancy. Three cases were detected at necropsy, 5 by mass radiography, and one accidentally during bronchoscopy. The latter 6 were all operated upon because of the suspicion of malignancy. There were no symptoms and no positive physical or laboratory findings. There is no characteristic roentgenographic picture. Even the presence of calcification may be deceptive. Because of the strong suspicion of malignancy, operation is indicated. A simple resection is adequate.—*Chondromatous hamartoma of the lung, C. V. Carlsen & W. Kiaer, Thorax, December, 1950, 5: 283.—(A. G. Cohen)*

Mesothelioma of the Pleura.—Primary tumors of the pleura are rare. The most common and distinctive type is a solitary fibrous growth, the identity of which has nearly been lost in the literature because of a profusion of names. It is suggested that they be called mesotheliomas, with the term 'solitary' or 'localized' to distinguish them from the even less common diffuse mesothelioma. They do not appear different in gross appearance from many other single peripheral lesions. Of 8 cases operated upon, 3 were intrapleural and pedunculated; they were benign. Five were intrapulmonary but with broad pleural attachments; they were all malignant.—*Solitary (localized) mesothelioma of the pleura, A. P. Stout & G. M. Himadi, Ann. Surg., January, 1951, 133: 50.—(W. H. Oatway, Jr.)*

Bronchoscopic Perforation Trachea and Bronchus.—Records of approximately 15,000 bronchoscopies indicated only one case each of instrumental perforation of the trachea and of a bronchus. Following a vigorous cough, the trachea was seen to have been lacerated. Subcutaneous emphysema appeared at once. An incision was made in the neck down to the trachea. This was packed lightly with a dry dressing. Large doses of penicillin were given. The condition subsided in a few days. A case of perforation of the left upper lobe bronchus occurred in 1940. Subcutaneous emphysema was seen on the following day. Sulfapyridine was given and recovery was uneventful.—*Perforation of the trachea and bronchus by the bronchoscope, W. Gordon, Thorax, December, 1950, 5: 339.—(A. G. Cohen)*

Complications of Bronchography.—A series of 220 bronchograms, mostly of young men, was reviewed. In 16 patients, a delayed reaction took place in one to two weeks. This was pulmonary in type and was characterized by cough, chest pain and malaise; there was pleural effusion in 5 and urticaria in 4. Roentgenographically, there was evidence of reaction around the residual oil. Recovery was complete. Several required a second bronchogram from which they did not suffer any reaction. All patients received preoperative potassium iodide without any reaction. Skin tests were not done.—*Delayed pulmonary complications of bronchography, P. W. Robertson & K. D. F. Morle, Lancet, February 17, 1951, 1: 287.—(A. G. Cohen)*

Tracheobronchial Aspiration.—Most cases of acute respiratory distress in newborn infants fall in one of 3 groups: (*1*) disturbance of central nervous origin; (*2*) obstruction, usually due to aspirated material; and (*3*) anomalies of the respiratory tract. The second group is the largest, and immediate intervention is indicated. In the absence of a trained endoscopist, the following simple tech-

nique can be used. A laryngoscope is inserted and the vocal cords are exposed. A No. 11 French ureteral catheter with a cylindrical tip, multiple openings on the sides, and an oblique open end is slipped between the cords to the desired depth in the tracheobronchial tree. The other end of the catheter is connected through a brass tubing to a suction apparatus. Suction is continuously applied except when the cords are passed. With practice the catheter can be passed without the aid of a laryngoscope. This method was used in 79 cases. The results have been good in every case due to obstruction by foreign material.—*A safe and positive method of tracheobronchial aspiration in the newborn, E. B. Emerson, J.A.M.A., October 21, 1950, 144: 613.—(H. Abeles)*

Esophageal Foreign Bodies in Children.—Of 400 patient with esophageal foreign bodies seen during twenty-five years in a childrens' hospital, 80 per cent were less than two years old. There were no symptoms in 40 cases. The common symptoms in order of decreasing frequency were vomiting, dysphagia, choking, pain, and drooling. Respiratory symptoms predominated in cases of long duration. Pain was the most common symptom of perforation. Coins, safety pins, and buttons were the most frequently swallowed objects. The most common site of lodgment was posteriorly at the level of the cricoid cartilage. Traction diverticula was a frequent complication in long-standing cases. Perforation and esophageal stenosis were also serious complications. The diagnosis should be made by history, roentgenographic examination in both the anteroposterior and lateral projections since 330 of the foreign bodies in this series were radiopaque, barium or lipiodol swallows, and esophagoscopy. Three patients died but rapid recovery was the rule when the diagnosis was made promptly and when attempts to remove the foreign body were begun early. In 33 instances the offending object passed uneventfully into the stomach.—*Esophageal foreign bodies, G. Boyd, Canad. M. J., February, 1951, 64: 102.—(E. A. Riley)*

Postoperative Analgesia.—Cholinergic substances enhance the effect of analgesic drugs. In patients who had undergone chest surgery, prostigmin was given in conjunction with pantopon; this made a 40 per cent reduction of the pantopon dosage possible. By this method interference with the cough reflex is prevented and expectoration is improved.—*Ueber eine Methode der verbesserte postoperativen Schmerzstillung Thorazoperierter, A. Frank, Wien. klin. Wchnschr., January 12, 1951, 63: 30.—(G. C. Leiner)*

ANTIMICROBIAL THERAPY

Streptomycin for Bronchial Tuberculosis.—Six hospitals participated in a cooperative study of the effects of streptomycin on tuberculous lesions of the trachea and bronchi. There was a wide variation in the extent and type of pulmonary involvement. The dosage of the drug was 1 to 2 gm. daily for four months. In 24 cases (68 per cent), there was great improvement at the time of the final bronchoscopy four to six months after treatment was begun. In 15 cases, the improvement was apparent as early as two months. If no improvement was seen at this time, then usually there was none eventually. There was greater improvement in cases with no pulmonary cavities. Bronchial stenosis was present at the onset in 15 cases and developed in 7 more during treatment. The sputum was converted to negative in 24 cases; some of these had also received collapse or resectional therapy. In 2 cases, the presence of masses of granulation tissue necessitated bronchoscopic removal.—*Streptomycin treatment of tuberculous lesions of the trachea and bronchi, Lancet, February 3, 1951, 1: 253.—(A. G. Cohen)*

Endometrial Tuberculosis.—Endometrial tuberculosis is essentially a silent lesion. If a suspicious lesion is discovered in curettings or biopsy, then another curettage is performed seven days before the expected menstrual period. Samples are sent for both histologic and bacteriologic study. In 18 cases, the diagnosis was established by both methods.

In 4 cases, histologic examination was positive while the bacteriologic findings were negative. The therapy consisted of intramuscular streptomycin, 1.0 gm., and oral *p*-aminosalicylic acid, 10.0 gm., daily for three months. Frequent biopsies of the endometrium are inadvisable. The first re-examination should be done three months after treatment has been completed.—*Tuberculosis of the endometrium, M. Haines, Lancet, February 24, 1951, 1: 436.*—*(A. G. Cohen)*

Genital Tuberculosis.—The latent form of genital tuberculosis in women is more common than the active form. It almost always leads to sterility as the result of tubal involvement. The disease arises in the mesenteric nodes then spreads into the Fallopian tubes. It may then spread to the endometrium. The condition may clear up spontaneously. The author reports 5 cases diagnosed by biopsy and one by culture. Treatment consisted of streptomycin given by daily injection, the dose totaling 40 to 45 gm. This regimen was effective. Following completion of the article, 6 additional cases were treated similarly with good results.—*Streptomycin in latent genital tuberculosis in women, I. Halbrecht, Lancet, January 13, 1951, 1: 85.*—*(A. G. Cohen)*

Primary Streptomycin-Resistant Tuberculosis.—An infant aged eleven weeks was found to have miliary tuberculosis from which it died in its twenty-fifth week. A culture of the gastric contents on admission contained tubercle bacilli which were highly resistant to streptomycin. The infant received a total of 11.6 gm. of streptomycin. A culture shortly before death likewise revealed a high degree of resistance. The mother was found to be tuberculous on the eighteenth day of the puerperium at which time the infant was separated from her. Sputum examinations were negative. She had never received streptomycin. It is assumed that the mother's infection was caused by a streptomycin-resistant organism which she, in turn, passed on to the infant.—*Primary streptomycin-resistant tuberculosis in a newborn child, J. E. Tinne & J. L. Henderson, Lancet, December 30, 1950, 2: 901.*—*(A. G. Cohen)*

PAS for Primary Tuberculosis.—*p*-Aminosalicylic acid (PAS) in daily doses of 0.60 to 0.75 gm. per kg. of body weight was given for three months to 28 children between the ages of two and six years with active primary tuberculosis. There were nineteen cases of segmental or lobar consolidation, 3 cases of ill-defined pulmonary infiltration, and 6 cases of voluminous hilar adenopathy. The clinical symptoms, especially the fever, regressed most often within the first two weeks of treatment. The general condition improved during the following few weeks. There was usually considerable regression of lesion on the roentgenogram during the first month and after three or four months the roentgenologic clearing was comparable to that usually achieved after 18 months of simple rest cure. The drug was well tolerated; skin manifestations were the only signs of intolerance and disappeared rapidly after interruption of treatment.—*L'acide para-amino-salicylique dans le traitement de la primoinfection tuberculeuse du jeune enfant, E. Lesné, L. H. Lafay-Coletzos, & C. Lefrancois, Semaine d. hôp. Paris, January 30, 1951, 27: 331.*—*(V. Leites)*

Resistance to PAS.—In a group of 23 patients treated for 70 days with *p*-aminosalicylic acid (PAS), 61 per cent had tubercle bacilli which were 5 to 100 times more resistant to PAS on Dubos medium than bacilli from untreated patients. After 182 days of treatment, the bacilli of all patients whose sputum still remained positive showed resistant strains. In order to demonstrate differences in resistance to PAS between strains from treated and untreated patients, smaller quantities of bacilli should be used for inoculation than for the determination of streptomycin sensitivity. Thus, in using liquid media of Dubos or Youmans the authors have inoculated 0.01 mg. of bacilli per 5 cc. of medium. Employing this technique, tubercle bacilli were considered resistant to PAS if they were not inhibited by 2.5 γ of PAS per cc.

This was based on the fact that no therapeutic effect was seen in patients whose bacilli were initially resistant to 2.5 γ *in vitro*. Likewise, patients who responded well to PAS ceased to do so when their bacilli were not inhibited by 2.5 γ *in vitro*. In a group of 37 patients, 11 per cent were found to be resistant to 2.5 γ per cc. before treatment was started. After 54 days of treatment with 20 to 25 gm. of PAS daily, 43 per cent of "positive" patients showed resistance; this percentage increased to 61 after 70 days, 88 after 126 days, and 100 per cent after 182 days. As with streptomycin, the presence of visible cultures in the medium does not mean that all inoculated bacilli are resistant. The proportion of resistant to sensitive strains may vary from 1 per 2,000 to 100 per cent. The association of PAS and sulfones delayed notably the emergence of resistance to PAS. Considering that resistance to PAS occurs frequently and early, the indications for this drug should be carefully studied; the duration of treatment should be limited to four or six weeks if given alone; combined treatment with streptomycin and sulfones is advisable.—*La résistance du bacille tuberculeux à l'acide para-aminosalicylique (PAS), N. Rist, P. Veran, B. Ballet, F. Grumbach, & R. Tricherau, Presse méd., January 13, 1951, 59: 21.*—(*V. Leites*)

Febrile Reaction to PAS.—In 8 patients *p*-aminosalicylic acid (PAS) produced marked febrile reactions. They occurred in various forms of pulmonary tuberculosis and developed most often in the second or third week of treatment. The daily dose did not seem relevant since it varied from 9 to 18 gm. in these cases. There was no correlation to the form of the drug as powder, granules, or tablets. The fever either progressively increased for several days or suddenly rose to 103° or 104°F. within a few hours each day. The fever fell rapidly and definitively when PAS was discontinued; it recurred immediately when the drug was restarted. The temperature elevation simulated exacerbations or complications of the disease process itself if the treatment was not interrupted.—*Les poussées fébriles du P. A. S., B. Kreis, A. Libert, F. Paquelin, & I. Abric, Presse méd., November, 1950, 58: 1285.*—(*V. Leites*)

PAS.—A total of 200 cases of pulmonary tuberculosis were treated with *p*-aminosalicylic acid (PAS); 42 received streptomycin also. It was believed that PAS did not enhance the effect of streptomycin. (*1*) Of 62 cases of chronic far advanced tuberculosis of the caseocavernous type, PAS had no effect in 30; 23 patients showed definite clinical improvement, the effects being as pronounced as those of streptomycin in similar cases. Only 9 patients in this group showed roentgenographic improvement. (*2*) Of 56 cases of fresh caseous pneumonic tuberculosis with cavitation, no effect was noted in 21; there was clinical improvement in 27; roentgenographic regression occurred in 8 cases. (*3*) In 12 cases of nodular disseminations, the superiority of streptomycin was particularly evident. PAS produced no effect in 2 cases, clinical improvement in 9, and roentgenographic improvement in one case. (*4*) In 6 cases of massive lobar consolidation, there was no roentgenographic change ascribable to PAS; clinical improvement was present in all cases. (*5*) In 5 cases of early infiltration, there was definite but incomplete clearing in 2 cases and no effect in 3. (*6*) In 14 cases of empyema, the follow-up period was short but the results seemed to indicate a favorable effect of PAS. (*7*) In 4 patients with grave primary tuberculosis, high fever, and marked constitutional involvement, PAS gave definite clinical results. Of the 200 patients, 60 per cent had gastrointestinal disturbances due to PAS. An additional 100 patients not included in this study were absolutely unable to tolerate the drug.—*Notre expérience du traitement de la tuberculose par l'acide para-aminosalicylique (PAS), A. Duroux, P. Masson, J. Marty, P. Tabusse, G. Ablard, & F. Bloch, Rev. de la tuberc., 1950, 14: 832.*—(*V. Leites*)

Mixed Infections in Bone Tuberculosis.—At the Tokyo Jikeikai Medical College, 110 mixed infections were found in tuberculous

lesions of the bones and joints. Of the complicating organisms, 48 per cent were identified as *Staphylococci*, 31 per cent as *Streptococci*, 13 per cent as *Ps. aeruginosa*, and 1 per cent each as *E. coli Diplococci*, and *B. proteus*. The *Streptococci* were sensitive to 0.006 to 0.012 units of penicillin per ml. and the *Staphylococci* to 0.25 to 1 0 units per ml. Treatment routinely consisted of 50,000 or 60,000 units of penicillin every three hours; higher doses were used for more resistant organisms. In 3 cases *Staphylococci* became more resistant to penicillin when small doses of the drug were employed.—*The infecting bacteria in mixed infections in bone and joint tuberculosis (Japanese), H. Sato, J. Antibiotics, November, 1950, 3: Supplement C, 11.*

Streptomycin for Bovine Actinomycosis.—Unusually favorable results have been obtained using streptomycin for actinomycosis in cattle. This was true even when bone was definitely involved and *Actinomyces bovis* was recovered from the lesion. Every day for three days 5 gm. of streptomycin in 10 cc. of distilled water were injected subcutaneously around the periphery of lesions. Additional injections were given at varying intervals. Of 10 cows treated, one died primarily from pneumonia and following abortion of a fetus, and one cow has shown a satisfactory response but the lesion has not fully cleared. The other 8 cows have had an excellent response, with clearing and arrest of all lesions of actinomycosis.—*Streptomycin in the treatment of actinomycosis, H. E. Kingman & J. S. Palen, J. Am. Vet. M. A., January, 1951, 118: 23.*—(*L. Hyde*)

Klebsiella Pneumonia.—Five cases of lobar pneumonia due to *Klebsiella pneumoniae* are reported. Four patients were treated with streptomycin; 3 responded satisfactorily, while the fourth patient died. The fifth patient was treated with aureomycin after treatment with penicillin failed to halt his downhill course. Prompt recovery followed the initiation of aureomycin treatment.—*Acute primary Klebsiella pneumonia, M. Nataro, D. Shapiro, & A. T. Gordon, J.A.M.A., September 2, 1950, 144: 12.*—(*H. Abeles*)

Influenza.—In a controlled study of the effect of aureomycin in the treatment of influenza A′, in 150 consecutive unselected cases occurring during an epidemic, the course of the illness in patients treated with this drug was not significantly different than that observed in patients who received penicillin or no chemotherapy at all (Authors' summary). —*Aureomycin in treatment of influenza: A controlled study, W. G. Thalmann, C. H. Kempe, J. A. Worrall, & G. Meiklejohn, J.A.M.A., December 2, 1950, 144: 1156.*—(*H. Abeles*)

Streptomycin and PAS in Experimental Tuberculosis.—Two groups of 24 guinea pigs were infected with a strain of streptomycin-resistant and streptomycin-sensitive tubercle bacilli. Each group was divided into 4 subgroups, one of which served as a control, the other 3 receiving streptomycin, *p*-aminosalicylic acid (PAS), or both. The daily streptomycin dose was 0.01 gm. the animals being sacrified on the twenty-ninth day of treatment. PAS, 0.2 gm., was given for one week by intramuscular injection and then continued in a dose of 0.2 gm. orally for a total of forty-two days. The combined treatment was carried out with the same dosages for forty-two days. All treatments were started on the sixteenth day after infection. The degree of infection was determined by the involvement of spleen, liver, and lungs. A maximal coefficient of 4 was allowed for each organ; the total for all 3 organs gave the index for the animal. The sum of indices for all animals in a subgroup divided by the number of animals gave the mean index of tuberculous infection. The control group infected with streptomycin-resistant strains had a mean index of 6, the one with streptomycin-sensitive strains a mean index of 3. The streptomycin-treated group infected with resistant strains had an index of 6.5 as compared to 0.2 in the animals infected with a sensitive strain. The PAS-treated group had

indices of 2.7 and 2.6, respectively. The animals receiving combined treatment showed a mean index of 2.1 for those with resistant strains and 0.4 for those with sensitive strains. The addition of PAS to streptomycin did not improve the results obtained with streptomycin alone in the presence of sensitive strains. In these experiments there was no emergence of resistance in the initially sensitive strains. Streptomycin-resistant strains, however, showed further increase in resistance from 540 γ per cc. to 1,740 γ per cc. This increase in resistance was somewhat inhibited by the addition of PAS. PAS alone did not modify the sensitivity of the resistant strains.—*Action de la streptomycine et du para-amino-salicylate de soude (P.A.S.) dans la tuberculose experimentale du cobaye, R. Maral & A. Blandin, Ann. Inst. Pasteur, May, 1950, 79: 677.—(V. Leites)*

Chlorophyll and Tubercle Bacilli.—Water-soluble derivatives of chlorophyll have a bacteriostatic effect *in vitro* on tubercle bacilli. No growth of tubercle bacilli took place in concentrations of 70 γ per cc. and 7 γ per cc. Partial growth was observed in a concentration of 0.7 γ per cc. The bacteriostatic potency of this extract was comparable to that of streptomycin. Chlorophyll extract gave good results in the treatment of fistulas, colliquative skin tuberculosis, and in local administration in tuberculous cavities. *Zur bakteriostatischen Wirkung wasserlöslicher Chlorophyllderivate gegenüber Tuberkelbazillen, E. Dissman & E. Iglauer, Wien. klin. Wchnschr., November 10, 1950, 62: 847.—(G. C. Leiner)*

LABORATORY STUDIES

Slide Culture of Tubercle Bacilli.—Homogenized specimens of sputum and gastric contents were used to compare the efficacy of the authors' slide culture method for tubercle bacilli with standard methods. An aliquot of each specimen was prepared in the usual manner and planted on three tubes of Petragnani's medium. These tubes were incubated for eight weeks before being reported as negative. A portion of each sputum sediment was smeared for microscopic examination. An aliquot of each homogenized specimen was heavily smeared on each of three slides which were treated with 6 per cent sulfuric acid, washed with water, and incubated in a liquid medium. One slide was removed on the second, one on the fourth, and one on the sixth day; each was stained and examined microscopically. Of the 973 sputums cultured, 87 (8.9 per cent) were positive; 36 were also positive on the initial smear, so that 51 were positive on culture only. Of 501 gastric specimens examined, 58 (11.6 per cent) were positive. The slide cultures gave 83 (57 per cent) positive results from the 145 positive specimens as against 112 (77 per cent) positive results by the routine method. Where the bacilli were not scanty initially, the methods gave similar results; where the initial smear was negative, the routine method gave more than twice as many positive cultures as the slide method. The number of specimens lost by contamination was high, 9 per cent for the slide cultures and 12 per cent for routine culture. The films also tended to come off the slides. When technically unsatisfactory specimens are excluded, the findings were approximately the same by either method. It takes more time to use the slide method, but the average time of incubation for the positive slide cultures was only three and one-half days as against thirty-seven days for the routine cultures.—*Efficiency of slide culture of tubercle bacilli, J. W. Berry & H. Lowry, Am. J. Clin. Path., November, 1950, 20: 1037.—(J. S. Woolley)*

Effect of Bovine Plasma Fractions.—The effect on the rate of subsurface growth of *M. tuberculosis* H37Rv produced by the addition of bovine serum and 12 bovine plasma fractions to a modified Proskauer and Beck synthetic medium was studied. All cultures were examined once daily and a record was made of the time when growth first became visible. The results show that only the pro-antithrombin fraction appeared to stimulate the rate of growth to the same degree as whole serum. Although the generation time, 14.4

hours, of the organisms was the same in whole serum and proantithrombin, the mass of growth appeared to be slightly heavier in the presence of serum than in the presence of proantithrombin. The other plasma fractions that favorably affected growth of tubercle bacilli were crystalline bovine albumin, fraction V albumin, and the globulin fractions IV-1, IV-3, 4, fibrinolysin (fraction III-3), and one lot of prothrombin (fraction III-2); all of these increased the rate of growth of the organisms 17.6 per cent over that found in the basal synthetic medium regardless of the concentration, except fraction IV-3, 4. This fraction appeared to be slightly toxic for the tubercle bacilli in concentrations of 1.0 and 0.5 per cent as shown by the longer generation time. Antifibrinolysin and the globulin fractions, II and III, increased the rate of growth of *M. tuberculosis* 12.2 per cent. The addition of an ultrafiltrate, which contained no precipitable protein, and fibrinogen (fraction I) had no effect on the rate of growth. The results themselves must also be considered from the standpoint of the purity of the protein fractions employed. Since these are not pure substances in the chemical sense, the possibility that impurities might account for some of the effects must be kept in mind.—*The effect of bovine plasma fractions on the growth of Mycobacterium tuberculosis var. hominis, A. S. Youmans & G. P. Youmans, J. Bact., November, 1950, 60: 581.*—(*F. G. Petrik*)

Growth of Mycobacterium Tuberculosis.—A study was made of the rates of growth of 23 recently isolated strains of virulent tubercle bacilli to determine (*1*) whether such strains varied significantly in their growth requirements, (*2*) whether their metabolic activities differed appreciably from those of *M. tuberculosis* H37Rv, and (*3*) whether bovine proantithrombin would stimulate the growth of strains of *M. tuberculosis* other than H37Rv to the same degree as whole bovine serum. The media used were (*1*) the modified Proskauer and Beck described by Youmans and Karlson, (*2*) the basal medium to which was added whole bovine serum to a concentration of 10 per cent, (*3*) the basal medium plus proantithrombin, 0.5 per cent, (*4*) the basal medium plus crystalline bovine albumin, 0.2 per cent, and (*5*) the basal medium plus sorbitan monooleate (Tween 80), 0.05 per cent, and crystalline bovine albumin, 0.2 per cent. From freshly isolated culture, 2 consecutive subcultures were made in liquid sorbitan monooleate albumin medium in order to obtain diffuse growth. After one week of incubation at 37°C., appropriate dilutions were made of the second subculture and inoculated into a set of 3 tubes of each of the liquid media. The time in days when the growth of each inoculum first became visible was plotted against the logarithm of the amount of inoculum. From the curve so obtained, the rate of growth and generation time could be estimated. Recently isolated strains of *M. tuberculosis* grew as rapidly as H37Rv in highly nutritious or protective liquid media. The strains grew most rapidly and uniformly in the basal medium containing beef serum and the basal medium containing proantithrombin with generation times of 13.2 to 15.7 hours. The strains grew less rapidly and less uniformly in the basal medium alone having generation times of 20.5 to 24.0 hours, the crystalline bovine albumin medium with generation times of 15.7 to 24.0 hours, and the sorbitan monooleate albumin medium with generation times of 27.8 to 67.4 hours. The rate of multiplication of all 13 strains tested was slower in the sorbitan monooleate albumin medium than in the basal medium alone.—*The growth of recently isolated strains of Mycobacterium tuberculosis var. hominis in liquid media, G. P. Youmans & A. S. Youmans, J. Bact. November, 1950, 60: 569.*—(*F. G. Petrik*)

Origin of Tuberculin-Sensitizing Factor.—*In vitro* there is a tuberculin affinity of leukocytes from both tuberculin-negative and tuberculin-positive hosts. White cells from nontuberculous subjects lyse if sensitized with tuberculin and exposed to a factor in plasma from tuberculin-sensitive subjects. The lytic "plasma factor" is present in the euglobulin portion of blood, is heat labile,

and requires complement for its specific effect. The lysis occurs within an hour. The present study was undertaken to determine the source of the "plasma factor." Lymphocytes, neutrophils, tuberculin, and plasma of normal and tuberculous subjects were mixed in various combinations. White blood counts and smears were made at once and the mixtures were placed in stoppered siliconized Wassermann tubes, rolled at 100 r.p.m. in a 37°C. incubator. Leukocytes from a tuberculous host, when washed free of, and resuspended in, normal plasma, were not affected by tuberculin within the first hour of exposure as they might be in whole tuberculous blood. Following more prolonged exposure to tuberculin there was rapid breakdown of some of the cells, suggesting that the cells themselves slowly liberated the "plasma factor" into normal plasma. Normal cells in normal plasma were mixed with the supernatant fluid of leukocytes from a tuberculous host and tuberculin was then added; some of the leukocytes lysed promptly, indicating the presence of "plasma factor" derived from the leukocytes. The active substance released by leukocytes from a tuberculous host was isolated by dialysis and precipitated with the euglobulins. This "plasma factor" isolated from cells caused destruction of normal leukocytes in the presence of tuberculin. Lymphocytes from tuberculous patients when incubated seven hours liberated "plasma factor"; neutrophils did not. The factor from lymphocytes was in the euglobulin fraction on dialysis and lysed normal leukocytes in the presence of tuberculin, although not intrinsically toxic for normal or tuberculous leukocytes in the absence of tuberculin. This is further evidence that lymphocytes are the origin of antibodies.—*The lymphocytic origin of a plasma factor responsible for hypersensitivity in vitro of tuberculin type, J. M. Miller & C. B. Favour, J. Exper. Med., January 1, 1951, 93: 1.*—(*J. S. Woolley*)

Tannic Acid and Erythrocytic Agglutination.—Bacterial components can be adsorbed onto erythrocytes to render them agglutinable by specific antibodies. It has been generally assumed that a bacterial polysaccharide is the sensitizing agent, for purified protein preparations have not been shown to be adsorbed by normal erythrocytes. Adsorption might occur in 2 distinct phases: (*1*) an alteration of the erythrocytic surface; and (*2*) the adsorption of other substances by the cells. Inulin was found to render sheep cells capable of adsorbing protein, thus making them agglutinable by the corresponding antiprotein sera but this effect was uncertain. Tannic acid agglutinates erythrocytes and was much more active in promoting the adsorption of protein by these cells. This phenomenon was used in modifying the hemagglutination test of Middlebrook and Dubos. Weybridge PPD, said to contain 5 per cent polysaccharide, 7 per cent nucleic acid, and 88 per cent protein, was a more satisfactory antigen than other PPD or tuberculin X4 (Lederle). Sheep red cells were pretreated with tannic acid, 1:20,000, and following sensitization were suspended in normal rabbit serum, 1:250, in saline solution instead of plain physiologic saline solution to prevent hemolysis. Dilutions of the test serum were also made in dilute rabbit serum-saline. Sera from 35 tuberculous and 10 nontuberculous patients were titrated by the hemagglutination technique, both with and without tannic acid pretreatment of the sheep red cells. All of the sera from tuberculous individuals that were positive by the usual technique also agglutinated cells pretreated with tannic acid; in most cases the titer of the serum was considerably higher by the latter method. One tuberculous serum showed no agglutination by either method. Sera from 8 nontuberculous individuals were negative by both methods; sera from 2 agglutinated cells, in both methods. Experiments were also carried out to determine whether tannic-acid-treated erythrocytes could take up antigenic proteins and be agglutinated by corresponding antisera. Streptococcic protein, ovalbumin, horse serum albumin and globulin, and chicken serum globulin were used. In each case sensitized cells were agglutinated by high dilutions of antiserum directed against the adsorbed antigen. The polysaccharide of

tuberculin may act as a mediator altering the erythrocytes somewhat as tannic acid does so that they adsorb other materials which, in turn, play the active part in fixing antibody.—*The adsorption of proteins on erythrocytes treated with tannic acid and subsequent hemagglutination by antiprotein sera, S. V. Boyden, J. Exper. Med., February 1, 1951, 93: 107.*—(*J. S. Woolley*)

Resistance in Experimental Tuberculosis.—Intranasal instillation of bovine tubercle bacilli in mice kills 90 per cent of the animals in 13 to 22 days. The pulmonary lesions are of a hyperacute type with intense alveolar exudation, many polynuclear leukocytes, and rapid bacterial multiplication; there is only a trace of a "pre-collagen" reaction of the alveolar wall or of fibroblastic organization around the alveolus. Ten per cent of the inoculated animals live longer. This spontaneous resistance is conditioned by certain genetic factors and can be reinforced by inbreeding. The lesions of the surviving animals are different with exudation of macrophages into the alveoli accompanied by interstitial or intra-acinous sclerosis; lymphocytes and plasma cells predominate without follicular organization. The bacilli found are rare, granular, and poorly stained. Thus, in mice there is a form of airborne tuberculosis with slow progression and certain traits in common with human phthisis. Histologically, the lesions have the characteristics of the species but the chronicity of the infection is evident. The morphology of the bacilli and probably also their biologic characteristics are modified. The study of the genetic causation of these facts may furnish an important contribution to our knowledge of the mechanism of resistance to tuberculous infection.—*Contribution experimentale a l'étude du terrain dans la tuberculose. La tuberculose aérogene de la souris a l'évolution prolongée, M. Bariety, A. Vittioz, & J. Sifferlen, Presse méd., December 25, 1950, 58: 1434.*—(*V. Leites*)

Isolation of M. Johnei.—An attempt was made to improve and simplify the methods of isolation and primary cultivation of *M. johnei*. A comparison of oxalic acid, antiformin, caustic soda, sulfuric acid, and tribasic sodium phosphate methods was made. A simplified oxalic acid method was most satisfactory for tissues such as lymph node, liver, lung, spleen, and intestines. For isolation of *M. johnei* from feces, however, the antiformin method, while not completely reliable, was better than any of the other methods tested. To Corper's egg yolk, American Trudeau Society's egg-yolk-potato medium, Finlayson's egg medium, Herrold's egg-yolk agar, Johnson's lymph node, and Dubos medium, 1 per cent of heat-killed *M. phlei* were added. Growth of *M. johnei* on the above media was compared with growth on Dunkin's liver-extract medium. It was found that simple media containing at least 50 per cent of egg yolk are more reliable than complex mixtures of whole egg and liver extract.—*Observations on the isolation of Mycobacterium johnei in primary culture, A. W. Taylor, J. Path. & Bact., October, 1950, 62: 647.*—(*H. J. Henderson*)

Immunization with M. Paratuberculosis.—In an earlier paper it was reported that 5 to 300 mg. of heat-killed *M. paratuberculosis* would elicit an immunologic response and an infiltration of considerable size at the site of injection in sheep. Since this earlier work, experiments were done using smaller quantities of bacteria ranging from 0.37 to 6 mg. of dried bacteria per sheep. The immunologic response was found to be essentially similar to that produced by the larger doses but the infiltrations at the site of injection were smaller. The complement-fixing antibody titer started to fall somewhat earlier in this series than in the earlier experiments with larger doses. The skin sensitivity to avian tuberculin developed at least as regularly and it lasted approximately as long as after the larger dose. The possible usefulness of this kind of vaccine for producing resistance to infections with *M. paratuberculosis* is being investigated.—*Immunization with heat-killed Mycobacterium paratuberculosis in mineral*

oil: II, B. Sigurdsson & A. G. Tryggvadottir, J. Bact., April, 1950, 59: 541.—(F. G. Petrik)

Protein Fractions in Tuberculin.—Protein fractions with different physicochemical and biologic properties have been isolated previously from unheated culture filtrates of a number of different strains of tubercle bacilli grown upon a nonprotein synthetic medium. The amino acid composition of fractions A and C with the most different properties were studied. By paper chromatography at least 10 amino acids and one or 2 unidentified spots, possibly peptides, were identified in both A and C fractions. Quantitative chemical analyses of each fraction showed more tryptophane by the Bates method and more phenolic groups by the Folin reagent in unhydrolyzed samples of the A than of the C fraction. On hydrolysis, however, still more phenolic groups appeared in the A fractions, but not in the C fractions, indicating that some of the phenolic groups in the A fractions are inaccessible until released by hydrolysis. In analogy with work by many investigators on other physiologically active proteins, it is interesting that this tuberculoprotein A fraction which contains some of these apparently combined phenolic groups is also the most potent fraction in regard to tuberculin activity and antigenicity.—*Analysis for certain amino acids in tuberculin protein fractions, F. B. Seibert & P. W. Kent, Brit. J. Exper. Path., December, 1950, 31: 48.—(H. J. Henderson)*

Oxygen Transport in the Lungs.—Fifty-five patients with pulmonary emphysema and fibrosis, who displayed an elevated alveolar-arterial oxygen gradient of 20 mm. of mercury or more, were studied in an effort to determine whether this defect could be attributed to increased difficulty of diffusion across the alveolar membrane or to unequal aeration of the alveoli. It was found that breathing low oxygen gas mixtures (11.5 and 18.7 per cent oxygen) resulted in a lessening of the alveolar-arterial oxygen gradient as compared with breathing air. A similar lowering of the gradient was noted during intermittent positive pressure breathing with compressed air. Breathing mixtures with high (27.8 per cent) oxygen content was accompanied by a further rise in the abnormally high gradient. It was believed that the more complete aeration of the alveoli resulting from intermittent positive pressure breathing and the increased ventilation associated with the breathing of low oxygen mixtures probably accounted for the lowering of the alveolar-arterial gradient that was noted. The defect in pulmonary emphysema and fibrosis thus appeared to be in poor distribution of inspired oxygen among the alveoli and increased resistance of the alveolar membrane to diffusion appeared to be of minor significance.—*Effect of high and low oxygen levels and intermittent positive pressure breathing on oxygen transport in the lungs in pulmonary fibrosis and emphysema, H. L. Motley & J. F. Tomashefski, J. Appl. Physiol., October, 1950, 3: 189.—(W. J. Osher)*

Oxygen Gradient in Normals.—Simultaneous determinations of the carbon dioxide and oxygen in arterial blood and in end-tidal air were carried out in normal resting and exercising subjects. No significant gradient could be demonstrated for carbon dioxide between the end-tidal air and the arterial blood, whereas, for oxygen, a mean resting gradient of 5.2 + 1.27 mm. of mercury was found to be present. The former observation was taken to indicate that end-tidal air was a good representative of functioning alveolar air. The oxygen gradient was consistently present to a significant degree but was found to vary inversely in magnitude with changes of oxygen consumption, minute ventilation volume, tidal volume, and physiological dead space produced by exercise.—*Normal variations in end-tidal air and arterial blood carbon dioxide and oxygen tensions during moderate exercise, M. Suskind, R. A. Bruce, M. E. McDowell, P. N. G. Yu, & F. W. Lovejoy, Jr., J. Appl. Physiol., November, 1950, 3: 282.—(W. J. Osher)*

Chemoreceptors and Oxygen Saturation.—The carotid bodies of rabbits were destroyed with or without section of the aortic depressor nerves. Absence of the chemoreceptors was determined by the lack of response to sodium cyanide and by histologic examination. Denervated and control animals were maintained in a low-pressure chamber at 400 mm. of mercury for approximately six hours per day, six days a week. After 150 cumulative hours, rabbits with carotid denervation showed an increase of the hematocrit above the control level of 39 to 72 per cent of oxygen capacity from 23 to 36 per cent, and of the red blood cell count from 23 to 92 per cent; the reticulocyte peak ranged from 4 to 12 per cent. Control animals showed no significant changes. Aortic nerve section had no influence on the blood picture during anoxia. Carotid denervation did not influence the hematocrit and reticulocyte response following hemorrhage or cobalt administration. The percentage of arterial oxygen saturation was measured while the animals breathed a graded series of mixtures low in oxygen. Animals with carotid and aortic or carotid denervation alone gave saturation values far below those of the control rabbits. Denervation of one carotid body yielded intermediate values. Aortic nerve section produced no change from the normal. The arterial pO_2 of carotid-denervated rabbits breathing mixtures low in oxygen was below that of the control rabbits, whereas the arterial pCO_2 was higher. The intense polycythemic response of the carotid-denervated rabbit at 400 mm. of mercury is a result of the marked depression of arterial pO_2 and of the percentage of oxygen saturation (Author's summary).—*Influence of carotid body removal on polycythemia and arterial oxygen saturation during discontinuous anoxia, W. S. Grant, Am. J. Physiol., January 1, 1951, 164: 220.*—(*G. C. Leiner*)

Helium and Gas Exchange.—Statistically significant increase in the oxygen consumption and carbon dioxide production of intact mice and in oxygen consumption by striated muscle, liver, ventricle, and sarcoma occurs when these animals and tissues are exposed to helium at atmospheric pressure (Authors' summary).—*Effect of helium on gas exchange of mice, S. F. Cook, F. E. South, Jr., & D. R. Young, Am. J. Physiol., January 1, 1951, 164: 243.*—(*G. C. Leiner*)

Lung Capacity and Height.—Studies of the total lung capacity and its subdivisions were carried out by measurements of the vital capacity and of the amount of nitrogen contained in the lungs after normal expiration. A correlation could be demonstrated between these and the standing body height. Constants were derived which could express the relationship of the residual capacity, the functional residual capacity, and the maximal capacity to the cube of the body height in a linear fashion. A graphic representation of this relationship was described so that any set of observations could be plotted and compared to standard data for normals.—*Studies of lung capacities and intrapulmonary mixing: Normal lung capacities, J. B. Bateman, J. Appl. Physiol., September, 1950, 3: 133.*—(*W. J. Osher*)

Antihistaminics and Respiratory Response.—The effect of antihistaminic drugs on the respiratory rate and minute ventilation was determined in anesthetized dogs both for room air and for hypoxic nitrogen-oxygen mixtures. Respiratory stimulation, as measured by these indices, was found after the administration of 100 mg. of Antistine, Benadryl, and Pyribenzamine. Doses of 10 mg. of Pyribenzamine and Dramamine caused similar but less marked effects while 0.4 mg. of Chlor-trimeton was ineffective. The ability to respond to hypoxia did not appear to be significantly changed in dogs who had received premedication with these drugs, although the data that had been obtained for Chlor-trimeton could not be confirmed.—*Influence of antihistaminics on respiratory response to hypoxia, W. L. Burkhardt, B. R. Eastman, & H. B. Hale, J. Appl. Physiol., July, 1950, 3: 29.*—(*W. J. Osher*)

Efficacy of Artificial Respiration.—The efficacy of the Schaefer, Holger Nielsen, and Eve methods of artificial respiration were compared as to the amount of tidal exchange that could be produced. This was inferred from the change of the end expiratory points registered on spirometric recordings of normal subjects before and during the application of artificial respiration pressure. The results were further checked by applying the Eve method to subjects made apneic by forced breathing of pure oxygen. Tidal volumes with the Schaefer method were found to have a mean value of 180 cc.; with the Holger Nielsen method, 450 cc.; and with the Eve method, 540 cc. It was concluded that adequate ventilation could be obtained only by the Holger Nielsen and the Eve methods.—*Efficacy of artificial respiration, E. Asmussen & M. Nielsen, J. Appl. Physiol., August, 1950, 3: 95.—(W. J. Osher)*

Phrenic Nerve Regeneration.—Section and primary anastomosis of the left phrenic nerve were carried out on 5 dogs. Immediately after this procedure, no motion of the left diaphragm was noted even with faradic stimulation of the proximal nerve segment. Return of motion could be noted fluoroscopically, however, in three to six months. Anatomical examination of the diaphragmatic musculature after this period revealed that it was normal both grossly and microscopically.—*Left phreno-phrenic anastomosis, N. C. Jefferson, C. W. Phillips, & H. Necheles, J. Appl. Physiol., September, 1950, 3: 161.—(W. J. Osher)*

Alveolar Dust Cells.—Alveolar dust cells can be studied in their normal forms and under experimental conditions in the albino mouse. They are attached to the alveolar walls by insertion into pores or sockets and derive their nutrition from the local capillaries. Eventually they become free and are eliminated through the bronchial tree. They never enter the connective tissue of the lung and are never found in the lymphatic system. They are not to be confused with connective tissue histiocytes which often take up dust particles.—*The dust cells in the lungs of the albino mouse, C. C. Macklin, Lancet, February 24, 1951, 1: 432.—(A. G. Cohen)*

Acute Cor Pulmonale.—By means of a cardiac catheter specially designed to facilitate experimental vascular obstruction, reversible pulmonary arterial occlusion was produced in intact anesthetized dogs. The obstructing balloon was usually placed in one of the main branches of the pulmonary artery; following inflation in some instances it protruded into and partially obstructed the main pulmonary artery. The degree of resistance to right ventricular outflow therefore was variable. Acute right ventricular hypertension was produced in all experiments, the pressure increasing from an average control value of 23/2 to 64/8 mm. of mercury. In 6 of the 14 experiments, right ventricular hypertension was maintained for the duration of the obstruction; in the other 8, the end-diastolic pressures continued to rise and the systolic and pulse pressures fell. These changes were interpreted as representing acute failure of the right ventricle. In the group of animals developing failure, the relationship of the right ventricular end-diastolic or filling pressure to the pulse pressure described a curve resembling that of the Frank and Starling laws. These observations extend the applicability of the Frank and Starling Laws to the acutely failing myocardium of the intact animal. It is difficult to explain the development of right ventricular hypertension in animals with the obstructing catheter completely within the main branch of the pulmonary artery. Apparently the unobstructed portion of the pulmonary vascular bed was unable to accommodate the total volume of blood flow under the acute conditions of the experiment. The electrocardiographic changes were chiefly those of ischemia resulting from acute myocardial dilatation and decreased left ventricular output. Right axis deviation did not develop, despite increases in right ventricular pressure as great as five times the control value. This is in accord with the

concept that axis deviation results from change in the position of the heart or change in functioning ventricular mass (Authors' summary).—*Acute cor pulmonale: An experimental study utilizing a special cardiac catheter, M. D. Dotter & D. S. Lukas, Am. J. Physiol., January 1, 1951, 164: 254.*—(*G. C. Leiner*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Tuberculosis in Kenya.—A tuberculosis survey of Kenya Colony was made between February, 1948 and February, 1949, using tuberculin tests, physical examinations, and sputum studies. The over-all sensitivity rates were high. There was a higher incidence of male than female reactors and also a higher incidence of reactors among the urban population. The disease incidence was estimated at 11.1 per 1,000, representing a total of approximately 58,000 unhospitalised cases of active pulmonary tuberculosis. Although extrapulmonary tuberculosis was frequent, it was apparent that pulmonary tuberculosis was the most prevalent manifestation of the disease. The survey showed that the majority of the adult natives had been infected with tuberculosis but demonstrated no evidence of clinical activity and were able to sustain a primary infection as well as adult Europeans. The acute fulminating type of tuberculosis was very common, however, and was postulated to be due to the high degree of allergy to tuberculoprotein which exists with little concomitant immunity. This renders the native of Kenya liable to an acute and destructive type of tuberculosis on reinfection.—*Tuberculosis in Kenya, W. S. Haynes, Brit. M. J., January 13, 1951, No. 4697: 67.*—(*E. A. Riley*)

Endobronchial Tuberculosis.—Of 270 persons in contact with infectious pulmonary tuberculosis examined by roentgenograms and bronchial lavage between 1948 and 1950 at the Furbush Dispensary in Havana, 20 per cent had roentgenographic lesions confirmed by positive bronchial lavage. In an additional 16 per cent, tubercle bacilli were demonstrated after bronchial lavage although the roentgenograms were normal. In these 14 patients bronchoscopy revealed infiltrative and/or ulcerative lesions of the tracheobronchial tree. Some of these patients were followed for two years without roentgenographic evidence of pulmonary involvement. Of these, 11 patients were men, 3 were women; they were 17 to 35 years old. All the patients had positive Mantoux tests but were asymptomatic. The tracheobronchial lesions responded well to streptomycin and cauterization with 10 per cent silver nitrate. These cases are thought to represent incipient tracheobronchial reinfection tuberculosis of the adult. It is considered inadequate to examine contacts of "open" cases by roentgenograms alone. The importance of bronchoscopy and bronchial lavage in these cases is emphasized.—*Début bronchique de la tuberculose de réinfection chez l'adulte, J. J. Castillo, Presse méd., December 25, 1950, 58: 1468.*—(*V. Leites*)

BCG Results.—During the 1948 BCG campaign in Montreuil, 4,000 vaccinations were performed. Of those vaccinated, 3,099 were children between the ages of three and fifteen years; 60 per cent of all tuberculin-negative children were vaccinated. BCG was administered by the method of multiple scarifications. The tuberculin test was positive two months later in 99 per cent of the cases. In 18 per cent of the persons, there was slight enlargement of the regional nodes; 0.67 per cent had true adenopathy, and some of the nodes suppurated. In 6 children (0.86 per cent) who had no exposure to tuberculosis, BCG reactions were observed in the chest. There were benign paratracheal and peribronchial adenopathy, lobar consolidation due to compression by lymph nodes, and "pleuro-pulmonary reactions." BCG appeared to be the only cause to which these phenomena could be attributed. At the end of the years 1946, 1947, and 1948, the number of registered cases of active primary tuberculosis had been 20, 21, and 24, respectively. In 1949, after the BCG vaccinations the number was 14, a decrease of 41 per cent.—*Premiers*

résultats de la campagne du B.C.G. dans la ville de Montreuil en 1949 apres 4000 (quatre mille) vaccinations, M. Fourestier & E. de Saint-Germain, Rev. de la tuberc., 1950, 14: 868.—(V. Leites)

BCG Vaccination.—A total of 1,350 nurses and 1,302 medical students were tuberculin tested with 82.6 per cent giving a positive reaction. The positive rate increased with age and with the year of training. Of 462 negative reactors, 429 (92.9 per cent) accepted BCG. The intradermal technique was used. The Mantoux test was performed after eight to ten weeks, during which time the subjects continued with their normal duties. The results on 317 subjects showed 97.2 per cent conversion. Many who were negative on the thirty-ninth day became positive by the seventieth day.—*B.C.G. vaccination of nurses and students in Edinburgh, H. G. H. Houghton & N. W. Horne, Lancet, November 11, 1950, 2: 583.—(A. G. Cohen)*

Incidence of Tuberculin Sensitivity.—Tuberculin tests were performed on all children up to thirteen years of age who were admitted to a hospital over a ten-year period. Positive reactions were obtained in 10.2 per cent in 1944 and 20.3 per cent in 1948, with an average of 14.2 per cent. The incidence was 2.4 per cent in the group up to one year of age, increasing to 41.8 per cent in the twelve- to thirteen-year group. Reversion of the Mantoux reaction was seen in 6 of 40 cases. Thirty-seven cases of tuberculosis showed negative Mantoux reactions. The mortality from tuberculosis was 62 per cent in infants less than one year of age, decreasing to 5 per cent in the older groups. The greatest reduction in incidence occurred at the third to fourth year. Meningitis caused 88 per cent of the deaths.—*Incidence of tuberculin sensitivity in hospitalized children, M. J. Lunn, Lancet, February 17, 1951, 1: 57.—(A. G. Cohen)*

Mass Radiography.—By the use of 4 units, a total of 97,250 miniature films were taken in one year. The cost per film was 4s. 6d. Cases sent for further investigation cost £3 8s. 10d. The cost to discover a single case of tuberculosis varied with the incidence rate in the tested group. Thus, with a rate of 0.35 per cent, the cost was £64 10s., while at 2.0 per cent, the rate was £11 5s. When only suspected cases were studied, the cost was lower. Of all new cases seen in a large chest clinic in 1949, only 18.5 per cent had been picked up in surveys. Mass radiography of the total population is almost impossible. It is advised that attention be concentrated upon the following groups: (*1*) workers in hazardous industries; (*2*) all school-leavers; (*3*) teachers and other personnel in contact with children; (*4*) entrants into the armed forces; (*5*) candidates for employment; (*6*) women attending antenatal clinics; (*7*) clinically suspicious cases; (*8*) contacts; and (*9*) persons desiring examination.—*The pattern of mass radiography, E. G. W. Hoffstaedt, Lancet, December 9, 1950, 2: 757.—(A. G. Cohen)*

Carcinoma in Chromate Workers.—The number of chromate workers among the male lung cancer patients of two Baltimore hospitals during the past fifteen to twenty years was compared with the number of chromate workers among other groups of male patients in these hospitals. Only those cases in which the diagnosis of primary cancer of the lungs or bronchi was confirmed by histopathologic examination were included. Eleven of the cancer patients had had an occupational exposure to chromium compounds; 10 of these had worked in a local chromate-producing plant. None of the patients in any of the control groups had reported an exposure to chromium compounds. Statistical analysis indicated that the percentage of lung cancer patients who had been exposed to chromates was significantly higher than would be expected on the basis of the control hospitalized groups. The percentage of the lung cancer patients who were employed at the chromate-producing plant was compared with the percentage of the employed male population of Baltimore

who were employed at the chromate-producing plant. Here again statistical analysis showed that the percentage of chromate workers in the lung cancer series was significantly higher than the percentage of chromate workers in the employed male population of Baltimore. Thus, these data confirm the general opinion expressed in the German literature and the conclusions of the mortality study made by Machle and Gregorius in this country, namely, that the number of deaths due to cancer of the lungs and bronchi is greater in the chromate-producing industry than would normally be expected (Author's summary).—*Pulmonary carcinoma in chromate workers: II. Incidence on basis of hospital records, A. M. Baetjer, Arch. Indust. Hyg. & Occup. Med., November, 1950, 2: 505.*—(*T. H. Noehren*)

Air Pollutants and Acute Diseases.—Data obtained from studies of the health of persons exposed to specific chemical contaminants of the air have not yielded any definite evidence that chronic inhalation of such chemical contaminants in low concentrations affects susceptibility to acute infections of the respiratory tract. Similarly, the few experiments which have been performed on laboratory animals have yielded chiefly negative results. The data available at present are insufficient to warrant any definite conclusions.—*Chronic exposure to air pollutants and acute infectious respiratory diseases, A. M. Baetjer, Arch. Indust. Hyg. & Occup. Med., October, 1950, 2: 400.*—(*T. H. Noehren*)

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*TEMPEL, C. W., FREDERIC, J. H. Jr., MARDIS, R. C., TOWBIN, M. N., and DYE, W. E. Combined intermittent regimens employing streptomycin and PAS, Am. Rev. Tuberc., 1951, 63, 295

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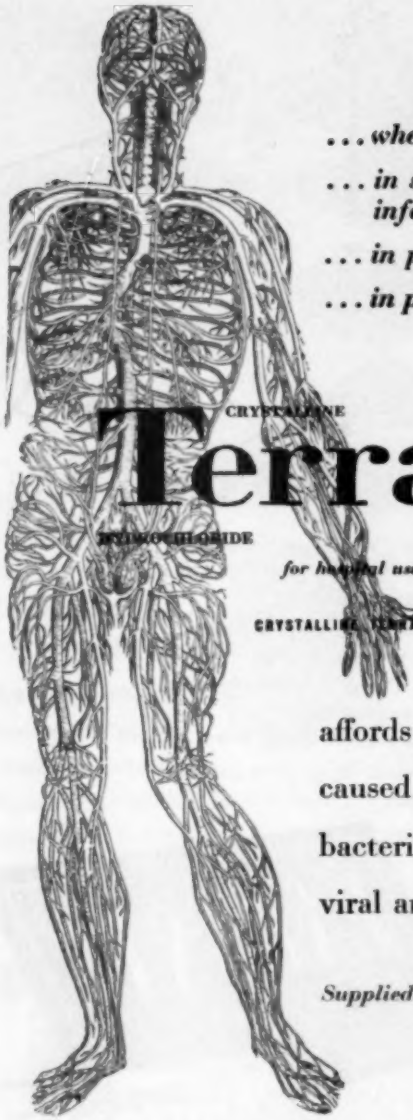

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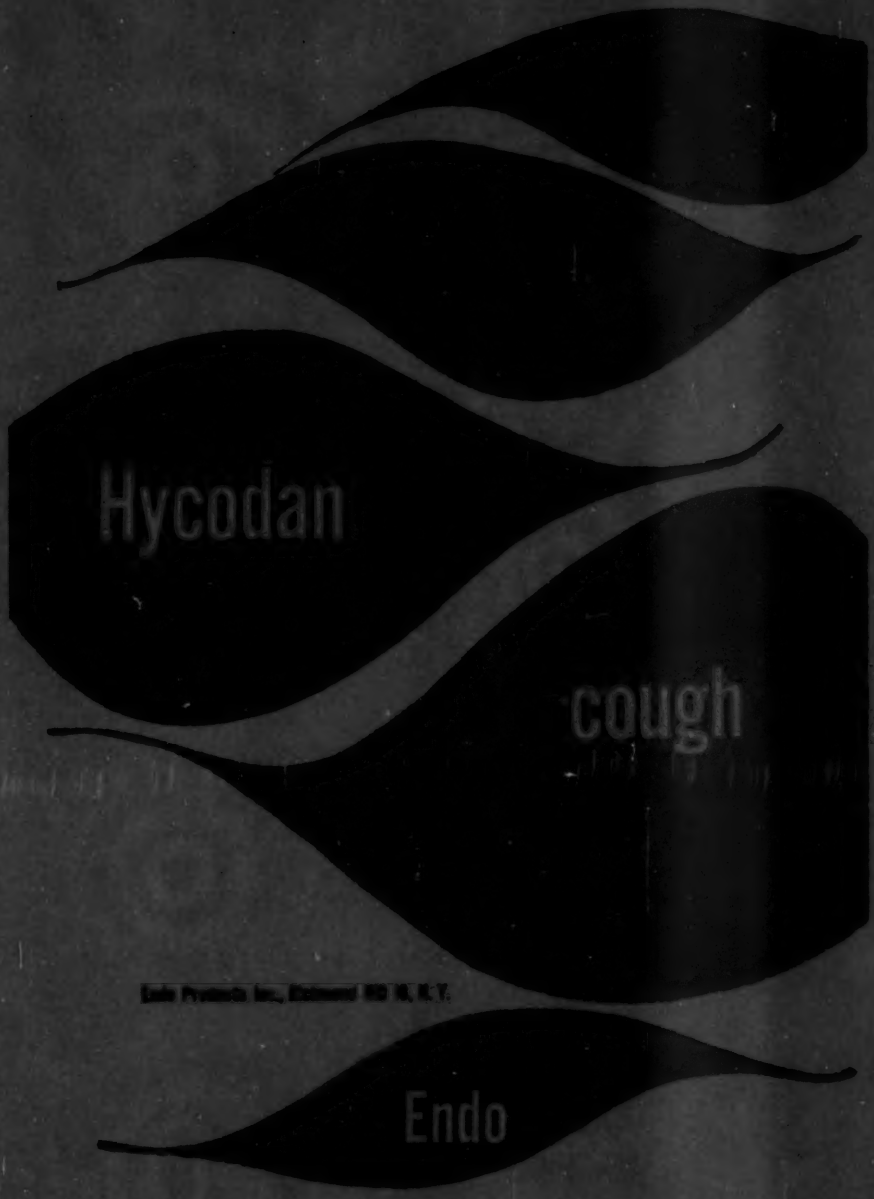
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